Partitioning and Lipophilicity in Quantitative Structure–Activity Relationships

by John C. Dearden*

The history of the relationship of biological activity to partition coefficient and related properties is briefly reviewed. The dominance of partition coefficient in quantitation of structure–activity relationships is emphasized, although the importance of other factors is also demonstrated.

Various mathematical models of *in vivo* transport and binding are discussed; most of these involve partitioning as the primary mechanism of transport. The models describe observed quantitative structure–activity relationships (QSARs) well on the whole, confirming that partitioning is of key importance in *in vivo* behavior of a xenobiotic. The partition coefficient is shown to correlate with numerous other parameters representing bulk, such as molecular weight, volume and surface area, parachor and calculated indices such as molecular connectivity; this is especially so for apolar molecules, because for polar molecules lipophilicity factors into both bulk and polar or hydrogen bonding components. The relationship of partition coefficient to chromatographic parameters is discussed, and it is shown that such parameters, which are often readily obtainable experimentally, can successfully supplant partition coefficient in QSARs.

The relationship of aqueous solubility with partition coefficient is examined in detail. Correlations are observed, even with solid compounds, and these can be used to predict solubility. The additive/constitutive nature of partition coefficient is discussed extensively, as are the available schemes for the calculation of partition coefficient.

Finally the use of partition coefficient to provide structural information is considered. It is shown that partition coefficient can be a valuable structural tool, especially if the enthalpy and entropy of partitioning are available.

It was well over 100 years ago that Crum Brown and Fraser (1) first suggested that biological activity could depend on a physiochemical property, namely aqueous solubility. At the same time (1869), Richardson (2) showed that the narcotic effect of primary aliphatic alcohols varied with their molecular weight. In 1893 Richet (3) confirmed Crum Brown and Fraser's prediction by showing that the toxicities of a variety of simple polar compounds such as ethers, alcohols and ketones were inversely related to their aqueous solubilities.

Just before the turn of the century, Overton (4) and Meyer (5) independently extended Richet's work and found that the narcotic effect of compounds of various classes increased with their oil–water partition coefficient; they postulated that the oil–water partitioning simulated the partitioning of a compound between the aqueous exobiophase and a lipophilic receptor. Partition coefficient, first defined by Berthelot and Jungfleisch (6) is, in practical terms, the ratio of concentrations at equilibrium of a solute distributed between two immiscible phases; the concentration in the more lipophilic phase is, by convention, the numerator. The term "immiscible" does not preclude the two phases having partial

miscibility. For example, water-saturated 1-octanol contains about 27% mole of water [the solubility of water in other common solvents is given by Leo (7)]. The term "partition coefficient" is restricted to defining the concentration ratio of the same molecular species, as was first pointed out by Nernst (8). The terms "distribution coefficient" or "apparent partition coefficient" apply to the ratio of total concentrations, including ionized and associated species. Partition coefficients quoted in this review are measured in the 1-octanol–water system unless otherwise stated.

The work of Meyer and Overton implied that the more lipophilic a compound, the better could it penetrate lipid membranes and reach an appropriate receptor site. The scene was thus set for further work on the relationship between lipophilicity and biological activity. In the event, Overton and Meyer were ahead of their time for there are no published records of any further such studies for many years.

In 1939 Ferguson (9) postulated what has become known as Ferguson's principle: that the toxic dose of a compound is a constant fraction of the aqueous solubility, or is at a constant thermodynamic activity. Extending this from toxicity to any biological activity, it should follow that the dose capable of eliciting a given biological response should increase as aqueous solubility

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increases. We shall see later that aqueous solubility is generally inversely related to partition coefficient, so that in effect Ferguson's principle can be construed as indicating that potency should increase with partition coefficient. Martin (10) has pointed out that this relationship should not, as is generally believed, be taken to imply a lack of specificity between substrate and receptor: the relative potency of congeners could well depend on their lipophilicity, while the specificity of the interaction will probably be due to electronic and steric effects (vide infra), including perhaps ionic and charge-transfer interactions and hydrogen bonding.

Over the years, medicinal chemists came to realize (11) that, despite the findings of Overton (4) and Meyer (5), one could not increase potency ad infinitum by simply increasing lipophilicity—hence the despairing cry "methyl, ethyl, butyl, futile." This failure of the potency–lipophilicity relationship was generally thought to be connected with aqueous solubility limitations. In 1948, Fieser and Richardson (12) demonstrated a curvilinear relationship between activity against P. lophurae in ducks and alkyl chain length in several series of naphthoquinone antimalarials, with activity reaching a maximum and then falling again as chain length increased. Fieser, Ettlinger, and Fawaz (13) showed, in effect, that the partition coefficient of the most active member of each species was approximately the same.

While relatively little progress was made during the first half of this century on correlating physicochemical and/or structural properties with biological activities, great strides were made, at least from 1940 onwards, in correlating structure with chemical reactivity, following the work of Hammett (14) in developing substituent constants related to electron-directing effects:

$$\log (Ka_X/Ka_H) = \rho\sigma_X \tag{1}$$

where Ka_H is the acid dissociation constant of a (parent) compound and Ka_X that of a derivative with substituent X; ρ is a series constant, and σ_X is the Hammett substituent constant of X.

In the 1950s and 1960s, various attempts were made (15)—without a great deal of success—to correlate biological activity with the Hammett constant. At about the same time Bruice, Kharasch, and Winzler (16) had generated de novo substituent constants and correlated these with biological response; this approach was followed by Zahradnik (17) and was expanded in the often quoted study of Free and Wilson(18).

A great leap forward was taken in 1962 by Hansch et al. (19), who demonstrated quantitative correlations between structural properties (partition coefficient and Hammett substituent constant σ) and biological activity. They showed that, for a series of 20 m- and p-substituted phenoxyacetic acids:

$$\log 1/C = 4.08\pi - 2.14\pi^2 + 2.78\sigma + 3.36 \tag{2}$$

where C is the concentration inducing a 10% growth in Avena coleoptiles in 24 hr, and π is a hydrophobic sub-stituent constant defined as $\log (P_X/P_H)$. We shall discuss this constant in more detail later. Hansch and Fujita (20) justified the use of a quadratic equation in π by the assumption of a normal Gaussian distribution of biological activity with $\log P$, since activity was often observed to rise and then fall again as partition coefficient increased. They added that they believed that the fall-off in activity at high $\log P$ values was due to the longer time needed for very lipophilic compounds to reach the site of action; this is in contrast to Ferguson's view that the effect is one of limiting aqueous solubility.

The justification for the use of $\log P$ (or π) is primarily that this is a free-energy-related term, from the van't Hoff isotherm:

$$\Delta G = -RT \ln P \tag{3}$$

and thus represents the free energy change during the transfer of the solute from water to nonaqueous phase.

Following the Hansch school's pioneering work in 1962 many hundreds of correlations between biological activities of all kinds and physicochemical and structural properties have been published. It is not appropriate in this review to discuss these relationships in detail. Hansch et al. have reviewed correlations rectilinear (21) and curvilinear (22) in $\log P$ or π, and suggest (21) that the former represent a special case of the latter with a restricted range of $\log P$.

Brief mention must be made of the incorporation of other than lipophilic parameters into quantitative structure–activity relationships (QSARs). Purcell and Testa (23) considered that the prime factors controlling transport to and interaction with the receptor are lipophilic, polar, electronic and steric. Transport may be considered to be controlled by lipophilicity for those compounds for which no active transport mechanism exists, but metabolism, which clearly can be controlled by electronic and steric factors (24), also governs the arrival of the active species at the receptor. Interaction with the receptor may be controlled by one or all of these factors. Hence many QSARs contain terms representing more than one factor. An excellent example of this is given by some recent work of Fujita (25) relating to the activity of N-chloroacetyl-N-phenylglycine esters against the rice plant:

$$pI_{50} = -0.33\pi - 0.95E_s^{ortho} - 0.62\sigma + 4.10 \tag{4}$$

with

$$n = 28$$
$$r = 0.959$$
$$s = 0.261$$

where I_{50} is the molar concentration that reduces shoot elongation to half the length of that of the control in 6 days and E_s^{ortho} is the Taft steric substituent constant, applied only to those compounds substituted in the ortho position.

Occasionally a biological response may be found not to depend on lipophilicity; this may occur, for example, with an in vitro response in which transport plays only

an insignificant part. An *in vivo* example is given by the adrenergic blocking activity of *N*-disubstituted 2-bromoalkylamines in the cat (*26*):

$$\log(1/C) = 1.113E_s^c + 3.566\sigma^* - 4.432n_H + 11.911 \tag{5}$$

with

$$n = 10$$
$$r = 0.986$$
$$s = 0.235$$

where E_s^c is the Hancock steric constant, σ^* is the Taft polar constant, and n_H is the number of hydrogens on the protonated amine. It may be noted that the statistics of Eq. (5) are dubious, since Topliss and Costello (*27*) have shown that, in order to minimize the risk of chance correlations, the ratio of observations to parameters should be at least 5:1.

Should lipophilicity play an important role in receptor binding, it may be that certain substituent positions in the substrate are more susceptible than others to such interactions. In such cases the QSAR should incorporate lipophilicity terms specific to those positions. Thus Li et al. (*28*) found that in the inhibition of human dihydrofolate reductase by 5-(X-benzyl)-2,4-diaminopyrimidines, 3- and 5-substitution in the aromatic ring produced different effects from 4-substitution:

$$\log (1/K_{app}) = 0.48\pi_{3,5} + 0.15\pi_4 + 4.10 \tag{6}$$

with

$$n = 38$$
$$r = 0.819$$
$$s = 0.301$$
$$F_{2,35} = 4.00$$

It is interesting to note that QSAR is being increasingly applied to problems of the environment. The bioconcentration (BC) of fungicidal dialkyl dithiolarylidene-malonates in *Oryzias latipes* L. has been shown (*29*) to be a function of lipophilicity, which is not unreasonable since the compounds may be thought of as partitioning between the fish and the aqueous milieu:

$$\log BC = 0.65 \log P - 1.17 \tag{7}$$

with

$$n = 9$$
$$r = 0.962$$
$$s = 0.197$$
$$F_{1,7} = 85.5$$

Published maximum noneffective doses (MND) of benzene derivatives were correlated (*30*) with octanol–water log *P* values:

$$\log MND = 023(\log P)^2 - 2.18 \log P$$
$$+ 0.84I_{CH_3} + 1.004I_{alkyl} + 2.06 \tag{8}$$

with

$$n = 18$$
$$r = 0.893$$
$$s = 0.505$$

Here I_x is an indicator variable describing the presence ($I = 1$) or the absence ($I = 0$) of fragment X.

Chemoreception has been shown to be markedly dependent on lipophilicity. Greenberg (*31*) investigated the correlation of olfactory threshold concentrations of various classes of compound with physiochemical properties. He found for alkanes in air, for example:

$$\log (1/C) = -0.24 (\log P)^2 + 2.57 \log P + 1.36 \tag{9}$$

with

$$n = 7$$
$$r = 0.97$$
$$s = 0.39$$

Briggs (*32*) has shown that the soil adsorption properties of a wide range of classes of compounds related to herbicides and pesticides are directly related to their octanol–water partition coefficients:

$$\log K_{om} = 0.52 \log P + 0.64 \tag{10}$$

with

$$n = 105$$
$$r = 0.95$$

where K_{om} is the distribution constant between soil organic matter and water.

Partitioning and Penetration

Since lipophilicity is a factor in so many QSARs, it is assumed that it is the prime mechanism by which xenobiotics are transported from the site of administration in an organism to the site of action and thence to the site of excretion. Although that assumption has not been proved absolutely, it can be assumed to have been proved by inference, from the work of Overton (*4*) and Meyer (*5*) onwards. The relationship can, following Hansch and Dunn (*21*), be expressed as:

$$\log P_{bio} = a \log P_{octanol} + b \tag{11}$$

where P_{bio} is the partition coefficient of a compound between the biophase and water.

This equation derives from the work of Collander (*33*), who showed that, for a congeneric series:

$$\log P_2 = a \log P_1 + b \tag{12}$$

where subscripts 1 and 2 relate to different partitioning systems.

Numerous reports have confirmed the validity of Eq. (11). For example, the distribution *D* of alcohols between human erythrocyte membranes and aqueous buffer was shown (*34*) to be correlated with their octanol–water log *P* values:

$$\log D = 1.003 \log P - 0.883 \qquad (13)$$

with

$$n = 5$$
$$r = 0.998$$
$$s = 0.082$$

Lien (35) showed that the gastric absorption of sulfonamides by the rat could be expressed by:

$$\log K = 0.314 \log P_{i\text{-amyl acetate}} - 1.159 \qquad (14)$$

with

$$n = 17$$
$$r = 0.942$$
$$s = 0.122$$

where K is the absorption rate constant. However, Lien also pointed out that relationships involving rates of partitioning are generally parabolic with respect to log P, as would be predicted by the Penniston model (36) of drug distribution; hence rectilinear relationships such as that of Eq. (14) are but limited segments of more general parabolic relationships. Thus, in the gastric absorption of barbiturates by the rat, the data are better described by a quadratic equation:

$$\log K = 0.268 \log P_{\text{CCl}_4} + 0.806 \qquad (15)$$

with

$$n = 16$$
$$r = 0.933$$
$$s = 0.123$$

and

$$\log K = 0.303 \log P_{\text{CCl}_4} - 0.068(\log P_{\text{CCl}_4})^2 - 0.725 \qquad (16)$$

with

$$n = 16$$
$$r = 0.958$$
$$s = 0.103$$

However, Plá-Delfina and Moreno (37) dispute the use of the parabolic model and offer an alternative which seems to fit better the observed biphasic relationships.

Naturally, the correlation of such parameters as penetration or absorption rate with lipophilicity has led investigators to search for QSARs in pharmacokinetics. Seydel (38) has recently reviewed this field and reports

numerous correlations, for example for a series of penicillins:

$$Vd_{\text{free}} = -63.8 \log P + 48.4 (\log P)^2 + 39.0 \qquad (17)$$

with

$$n = 7$$
$$r = 0.99$$
$$s = 17$$

and

$$\log \text{Cl} = 0.58 \log P - 0.85 \qquad (18)$$

with

$$n = 7$$
$$r = 0.92$$
$$s = 0.25$$

where Vd_{free} is the volume of distribution corrected for protein-binding and Cl is the clearance, both in the rat.

The dependence of penetration on partitioning has led to a number of attempts to model the distribution of xenobiotic within an organism. Penniston et al. (36) devised a nonsteady-state model based on rates of partitioning (partition coefficient being by definition the ratio of the forward and reverse partitioning rate constants). They assumed, for simplicity, that the product $k_1 k_2 = 1$. This is in fact not so (39), and the validity of the model has consequently been queried by Kubinyi (40), who showed (41) that:

$$k_1 k_2 = \frac{c^2 P}{(\beta P + 1)^2} \qquad (19)$$

where c and β are constants for the system. It is, however, the view of Dearden and Townend (42) that the model is valid, the assumption of $k_1 k_2 = 1$ simply altering the spread of the results.

By setting up and solving differential equations for the transfer to and from each compartment of the model, following initial administration of unit dose to compartment 1 at zero time, Penniston et al. were able to obtain the concentration (C) in each compartment as a function of time and partition coefficient. They showed that a plot of log C versus log P was approximately parabolic and used this to justify the use of quadratic equations in log P or π to describe the variation of biological response within a congeneric series. The initial increase of penetration rate (or concentration at the site of action at a fixed time after administration) with partition coef-
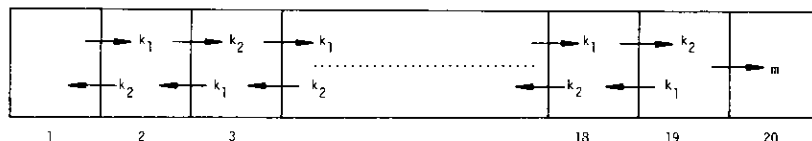

FIGURE 1. Nonsteady-state model of Penniston et al. (36).

ficient is consistent with the observation of Collander (43) that:

$$\log \text{Pen} = a \log P + b \qquad (20)$$

where Pen is penetration rate. Collander, however, studied compounds of low partition coefficient and so did not observe the decrease of penetration rate at high P values. Penniston et al. ascribed this fall-off to a decreasing ability of compounds to leave lipid membranes for subsequent aqueous compartments as P increases. Thus the concept of an optimal partition coefficient (P_0) giving maximal biological response arises. Penniston et al. pointed out that P_0 decreases as the number of partitioning steps in the model increases. Tute (44) has related this to the complexity of the "random walk" of compound from the site of administration in an organism to the site of action, pointing out that $\log P_0 \approx 6$ for bactericides active against Gram-positive bacteria, while $\log P_0 \approx 4$ for those active against the more complex Gram-negative bacteria.

McFarland (45) devised a model based on probability and demonstrated that the probability of a drug reaching a receptor site is a function of its partition coefficient and the number of intervening aqueous-lipid interfaces. Like the Penniston model, McFarland's model generated approximately parabolic relationships between (in McFarland's case) the probability of a molecule arriving at a receptor in a given time and $\log P$. All McFarland's curves showed $\log P_0 = 0$, which, as we have seen, is not the case in practice.

Higuchi and Davis (46) developed an equilibrium model based on consideration of the relative lipophilicity of the biophase and the receptor, and generated biphasic (but not necessarily parabolic) relationships between activity and carbon chain length (lipophilicity). Only when receptor lipophilicity is less than general biophase (lipoidal) lipophilicity does the model generate approximately parabolic curves. Curves reaching a plateau are obtained when the lipophilicities of receptor and lipid are equal. Such curves are sometimes observed in practice, but the conditions required by the Higuchi-Davis model seem too specific for the model to be very realistic.

Noting that many QSARs are not true parabolae, Franke (47) proposed that binding of the hydrophobic chain of a drug to a complementary site adjacent to the receptor would increase biological response by encouraging receptor binding; however, if the size of the molecule surpassed the size of the binding area, loss of activity would result from any further increase in lipophilicity. Thus Franke envisaged a rectilinear positive slope of such a QSAR and a parabolic peak and negative slope, each part of the QSAR described by a separate equation. He proposed that a positive slope of ca. 0.5 indicated adsorption onto a protein surface, since such low slopes are found for the correlation of binding constants to proteins with $\log P$ values (40), while a slope of ca. 1.0 indicated transfer of the drug molecule into a hydrophobic pocket. While the importance of protein-binding in drug activity should not be ignored, it

must be pointed out that Franke's theory calls for a specific type of increase in lipophilicity, via increase in alkyl chain length. In many congeneric series this is not the case. Secondly, the theory requires adjacent complementary hydrophobic sites, which may not always be present. Thus, the theory cannot be considered as having general applicability.

Yalkowsky and Flynn (48) considered steady-state transport in a water–membrane–water model. They predicted that under these conditions the flux across the membrane (which they took to be a measure of biological activity) would rise *ad infinitum* as chain length (i.e., $\log P$) increased. However, they pointed out that in practice two other effects would come into operation to prevent this. First, at some chain length or $\log P$ value, diffusional control of the overall transfer rate would become dominant (49), which would cause the activity to level off, since diffusion is only slightly dependent on molecular size. Second, as chain length increased, aqueous solubility would fall and this would reduce the flux. Hence, the overall relationship is similar to that predicted by other models. This model would be applicable to prolonged-release drug formulations, or continuous infusion, or organisms exposed to more or less constant concentrations of environmental pollutants. It is not, however, applicable to single-dosage situations. Hansch (50) has pointed out that if lack of water solubility caused activity to fall in such cases, one would expect a common $\log P_0$ value for the very lipophilic (poorly water-soluble) drugs active against both Gram-positive and Gram-negative bacteria. In fact, $\log P_0 \approx 4$ against Gram-negative bacteria and $\log P_0 \approx 6$ against Gram-positive bacteria. Furthermore, Dearden and Patel (51) have shown that a physical model comprising eleven alternate stirred aqueous and octanol compartments shows an approximately parabolic dependence of $\log C$ on $\log P$, where C is the concentration in the nth compartment at a given time after single-dose administration in solution in the first aqueous compartment.

Hyde (52) developed an equilibrium model base on receptor occupancy theory, which led to the equation:

$$\log(1/C) = -\log (a + 10^{-\pi}) \qquad (21)$$

where C is the concentration required to produce a specific response. Equation (21) generates a curve rising and reaching a plateau, as lipophilicity (π) increases. A number of experimentally observed QSARs are of this form, including some to which quadratic equations have been fitted on the assumption that at a sufficiently high partition coefficient, activity must eventually fall. However, the Hyde model cannot be considered of general applicability, since so many QSARs show a fall-off of activity at high lipophilicity.

Since it is generally assumed that only nonionized forms of molecules can penetrate lipid membranes and since many drugs are ionizable, Martin and Hackbarth (53) developed an equilibrium model, or rather a series
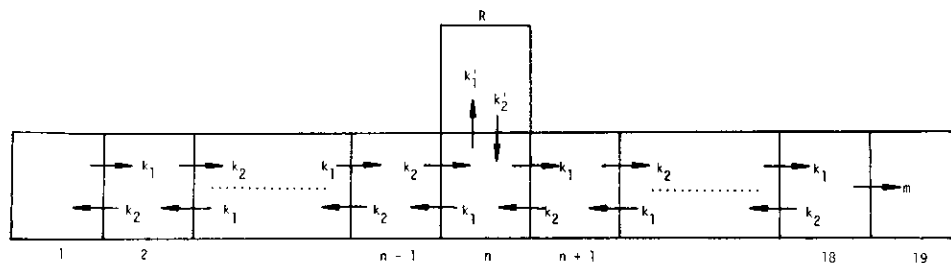
FIGURE 2.   Modified Penniston model.

of models, to take ionization into account. They obtained a number of equations for different sets of conditions and showed that under many of those conditions, paraboliclike curves were obtained. For example, with a model comprising one aqueous compartment, one non-aqueous compartment and a receptor, and assuming that only the neutral form of the drug interacted with the receptor, they obtained:

$$\log(1/C) = \log\left[1 + dP^C + \frac{1}{aP^b (1 - \alpha)}\right]^{-1} + x$$

(22)

where a, b, c, and d are constants, x is the proportionality constant between amount of drug at the receptor and potency and α is the degree of ionization.

In empirical terms, ionization may be accounted for by using the apparent rather than the true partition coefficient (i.e., the ratio of total concentrations at, say, physiological pH) in a QSAR. Thus, Moser et al. (54) showed that for a series of phenylbutazone analogs, variation of anti-inflammatory activity could be described by the equation:

$$\log (1/C) = -2.10 + 0.77 \log P' - 0.57 (\log P')^2$$

(23)

with

$n = 16$
$r = 0.798$
$s = 0.255$

where P' is the apparent partition coefficient at pH 7.4. Alternatively, a pK_a term can be included in the equation, although pK_a is generally used as an electronic term to represent electron-directing substituent effects. In Eq. (24), pK_a is used to correct for ionization (38):

$$\log k_m = -0.21 \log P + 0.13 pK_a - 1.29 \quad (24)$$

with

$n = 10$
$r = 0.90$
$s = 0.18$

where k_m is the rate constant for in vivo N^4 -acetylation of sulfonamides in the rat.

It seemed to us, on examining the various models, that that of Penniston et al. (36) was at once the most realistic and the most flexible. It is not a quantitative model, in that it does not generate equations to which experimental data can be fitted. But it can be adapted to model single or multiple administration, continuous administration, dissolution, equilibrium conditions and multiple receptor binding, for example. Perhaps most importantly of all, it can be used to examine the effect of time after administration upon biological response—a factor which has been sadly neglected.

The model as we use it can be represented by Figure 2. Compartment 1, which is aqueous, represents the site of administration, and can handle single, multiple or continuous administration and solubility limitation; it can also be adapted to include a dissolution step. One or more side-compartments, representing receptors, can be incorporated as required. The final compartment is aqueous and represents excretion; it can, of course, be made reversible if an equilibrium model is needed.

It is not normally necessary to use a receptor side-compartment, since similar results are obtained if con-
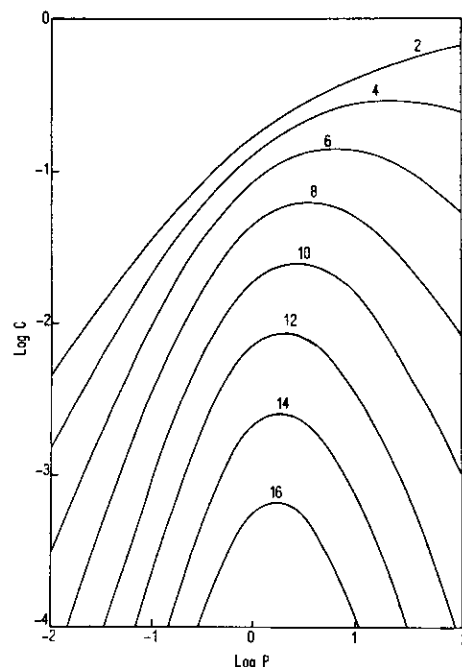
FIGURE 3.   Variation of concentration in the nth compartment with partition coefficient at a given time (t = 10) after dosage (Dearden and Townend modification of the Penniston model).

centrations in the nth compartment are followed. Figure 3 shows the variation of concentration with $\log P$ ($= \log k_1/k_2$) at a fixed arbitrary time after a single dose has been administered in compartment 1 (*55*). It will be seen that, as Penniston et al. (*36*) reported, $\log P_0$ decreases as the number of partitioning steps to the "site of action" increases. As well as this indicating different optimal lipophilicities for organisms of different complexity (*44*), it can be taken to show that different routes of administration will result in different lipophilic requirements. Thus, for analgesic analogs of paracetamol (acetaminophen), Dearden and Tomlinson (*56*) found $\log P_0 = 1.48$ for oral administration to mice, while Dearden and O'Hara (*57*) found $\log P_0 = 0.90$ for subcutaneous administration. Figure 4 shows how $\log P_0$ varies, within a given compartment, with time after dosage (*50*). The reason for this variation is that compounds with different lipophilicities move at different rates through an organism. So far as is known, there is no experimental confirmation of this prediction. It is interesting, although confusing, to note that Cooper, Berner, and Bruce (*58*), in an analysis of the Penniston model, concluded that it predicted that $\log P_0$ decreased with both time after dosage and the number of partitioning steps.

A related aspect is the variation of time to maximal concentration in a given compartment. Dearden and Townend (*55,59*) showed that this took an approximately parabolic form, being high for compounds of very low and very high lipophilicity, and low for intermediate compounds. There is ample experimental evidence to support this prediction. For example, the results of Kutter et al. (*60*) for the effects of morphine-like analgetics

for P measured in heptane-buffer, pH 7.4, in the rabbit can be correlated thus:

$$t_{max}(\text{min}) = 0.660 \ (\log P)^2 + 0.826 \log P + 3.457 \quad (25)$$

with

$$n = 11$$
$$r = 0.879$$
$$s = 3.103$$

The model also predicts that maximal concentration in a given compartment rises and then levels off as $\log P$ increases (i.e., curves similar to those generated by the Hyde model are obtained). Again, there is experimental confirmation of this prediction, from an investigation of blood platelet inhibition by aspirin derivatives (*61*).

Duration of action of a compound is often considered to be related to metabolism, but for compounds which are not metabolised appreciably, the model predicts an approximately parabolic relationship with lipophilicity, with compounds of intermediate lipophilicity having the shortest duration of action (*42*). Although duration of action data are scarce in the literature, those that there are confirm the model prediction. For example, the results of Kutter et al. (*60*) and Herz and Teschemacher (*62*) concerning the analgesic effect of morphine analogs administered intravenously in rabbits can be correlated thus:

Duration (hr)

$$= 0.149 \ (\log P)^2 + 0.053 \log P + 0.449 \quad (26)$$

with

$$n = 11$$
$$r = 0.981$$
$$s = 0.324$$

for P measured in heptane-buffer, pH 7.4. Occasionally, QSARs containing two peaks have been observed. Franke and Kühne (*63*) extended Franke's original hypothesis (*47*) to account for this, by postulating two adjacent receptors; initial activity involves activation of one receptor only and as the chain length of the molecule increases, activity falls off, but increases again when the chain is long enough to interact with the second receptor site. This theory is vulnerable to the same criticism as that of Franke's earlier theory regarding biphasic curves (*47*). We prefer, as a general theory, the concept of two different receptors having different lipophilic requirements and showed (*64*) that the Penniston model, modified by two receptor side-compartments, could account satisfactorily for such double-peaked QSARs.

The above cases show that the Penniston model, suitably modified as appropriate, can account for virtually all aspects of quantitative structure–activity relationships involving only lipophilic parameters.
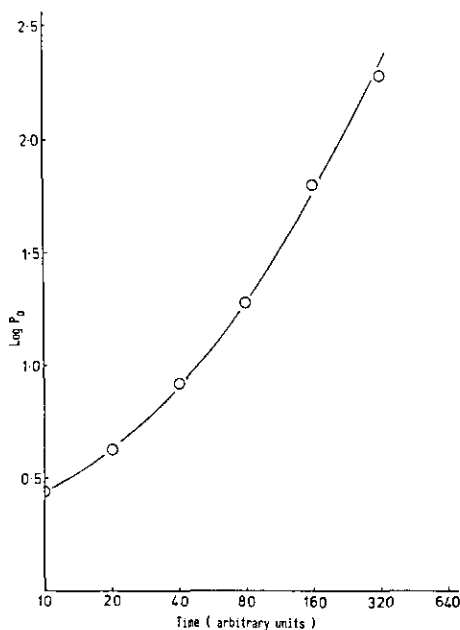

FIGURE 4. Variation of optimal partition coefficient with time after dosage (Dearden and Townend modification of the Penniston model).

It may be argued, following Yalkowsky and Flynn (48), that the model is invalid because it takes no account of diffusion and solubility which, as Yalkowsky and Flynn showed, become rate-limiting (for their model at least) at high lipophilicity. But, as already mentioned, the physical model of Dearden and Patel (51), consisting of eleven stirred compartments containing alternately water and 1-octanol, yielded approximately parabolic curves for log C vs. log P after single-dose administration in solution in the first compartment. Experimental confirmation was thus obtained for the postulate that biphasic QSARs can be interpreted purely in terms of control by a partitioning mechanism; it is not necessary, at least for the single dose situation, to invoke diffusion or solubility limitations, important though these may be in some circumstances.

This review of QSAR modeling would not be complete without reference to the work of Kubinyi. He observed that many so-called parabolic QSARs in fact appeared rather to consist of straight ascending and descending sections joined by a curvilinear section in the region of the peak. From a reconsideration of the McFarland (45) and Higuchi and Davis (46) models, Kubinyi derived his bilinear model (65) which yields the general equation:

$$\log (1/C) = a \log P - b \log (\beta P + 1) + C \quad (27)$$

The β term was introduced to permit log P_o to have values other than zero. Kubinyi hypothesized that β was related to the relative volumes of lipid and aqueous compartments in the organism; in support of that, we have shown (Dearden and Townend, unpublished work) that with the Penniston model, log P_o of the generated curves varies as the lipid/aqueous volume ratio is altered. It may be noted, however, that recently van de Waterbeemd has pointed out (66) that β can be used in membrane characterization and in terms of artificial (i.e., organic solvent) membranes is related to the viscosity (η) of the solvent:

$$\log \beta = -0.502 \log \eta + 0.156 \quad (28)$$

with
$$n = 9$$
$$r = -0.961$$
$$s = 0.130$$
$$F_{1,7} = 84.65$$

Kubinyi showed that his equation often proved a better fit to experimental data than did the quadratic equation. For example, for the hemolytic activity of homologous α-monoglycerides in aqueous solution, the bilinear model gives (41):

$$\log (1/C) = 0.993 \log P$$
$$- 2.212 \log (\beta P + 1) + 1.149 \quad (29)$$

with

$$\log \beta = -3.454$$
$$\log P_o = 3.36$$
$$n = 7$$
$$r = 0.999$$
$$s = 0.057$$

For the same data, Hansch and Clayton (22) give:

$$\log (1/C) = -0.36 (\log P)^2 + 2.43 \log P - 0.27 \quad (30)$$

with

$$\log P_o = 3.36$$
$$n = 7$$
$$r = 0.987$$
$$s = 0.152$$

In many examples, like the one above, the difference in fit of the two equations is marginal, and perhaps in such cases the quadratic equation is to be preferred because it is simpler to use; the Kubinyi equation requires an iteration procedure in order to solve for β. Where the bilinear equation really scores, however, is in cases where the ascending and descending sections of the QSAR have markedly different slopes, or where a plateau rather than a descending section is observed. Kubinyi (40) has stated that the Hyde equation (52), which describes a plateau, is a special case of Eq. (27).

Kubinyi has also (41) investigated the "QSAR" curves generated by a large number of multicompartment partition models of both the equilibrium and the nonequilibrium types, and with and without side compartments. His findings are in general similar to our own, but a particularly interesting observation is that, using a nonequilibrium side-compartment model (Fig. 5), the curve generated by plotting log (concentration in side-compartment) vs. log P is asymmetrical, with the descending arm of lower gradient than the ascending arm, in line with many experimental QSARs.

Berner and Cooper (67) have recently applied diffusion theory to the partitioning process. Their model predicts a maximum in the curve of $C_R(t)$ vs. log P, where $C_R(t)$ is the concentration in the receptor compartment at time t, in much the same way as does the Penniston model. They found it necessary, however, to introduce shunt pathways to make the model more realistic.

Other equations to model the variation of biological activity with lipophilicity have been proposed by Wagner and Sedman (68) and Seydel and Schaper (69).
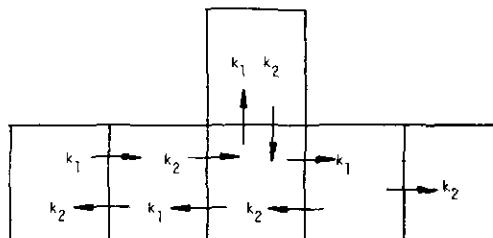

FIGURE 5. Nonequilibrium side-compartment model.

Choice of Solvent in Partitioning

Partition coefficient may be measured in any binary liquid system displaying at least some immiscibility. A study of the literature shows that a very wide range of lipophilic phases has been used, but the lipophobic phase is almost invariably aqueous. Despite the large number of lipophilic phases used, the majority of partiion coefficients are nowadays measured in octanol–water, largely as a result of Hansch's decision to use that system (70). Leo, Hansch, and Elkins (71), in their comprehensive review of partitioning, summarized the rationale behind the use of the octanol–water system. 1-Octanol, having a polar head and a hydrophobic alkyl chain, resembles the lipids of biological membranes. Also, a wide range of compounds is soluble in octanol, compared with, say, a hydrocarbon. Octanol dissolves 27% mole of water, and so hydrogen bonds need not be broken during the transfer of a hydrated drug molecule from the aqueous to the organic phase; hence the partition coefficient should be a measure largely of hydrophobicity, rather than including dehydration, as would be the case with hydrocarbon solvents. In support of this argument, Franke, Kühne, and Dove (72) have recently shown that while nitrogen–oleyl alcohol and nitrogen–water partition coefficients were very sensitive to subtle solvation features, oleyl alcohol–water partition coefficients were not. Octanol is widely and cheaply available and has no specific near ultraviolet absorption (many partition coefficients being determined spectrophotometrically). Octanol has a low vapor pressure relative to hydrocarbons such as cyclohexane and isooctane. The hydrophobic substituent constant π and the hydrophobic fragmental constant f which enable the calculation of partition coefficients, both refer to the octanol–water system. Perhaps most importantly from a QSAR standpoint, it works well. That is, good correlations are achieved between biological activities and octanol–water partition coefficients. It is only occasionally that one finds a better correlation using say, hydrocarbon–water system, as did Lien and Tong (73) for the absorption of phenylboronic acids into human skin:

$$\log C = 0.417 \log P_{benzene} - 2.463 \qquad (31)$$

with
$$n = 7$$
$$r = 0.954$$
$$s = 0.148$$

$$\log C = 0.573 \log P_{oct} - 3.749 \qquad (32)$$

$$n = 8$$
$$r = 0.907$$
$$s = 0.227$$

Octanol–water partition coefficients are generally less sensitive to temperature than are those of hydrocarbon–water systems, so that accurate temperature control of partitioning is less crucial. [Most partition coefficients are measured at (unspecified) "room temperature".]

Disadvantages of octanol are: thermodynamically it is a complex substance, rendered even more so by its high water content at saturation. The solubility of water in octanol varies appreciably with temperature (74), casting doubt on van't Hoff determination of the thermodynamics of partitioning. It is difficult to purify (commercial samples often containing ultraviolet-absorbing material). It may react with some acidic solutes to form esters (75). Rytting, Davis, and Higuchi (76), while conceding that a polar organic solvent is often more suitable for a QSAR study, nonetheless recommend the use of a noninteracting (hydrocarbon) organic phase on the grounds that the results should be more revealing.

It is the opinion of this writer that as the octanol–water system is the system of choice for practical purposes, we should use that system, at the same time seeking to unravel its complexities by fundamental investigations, including, if necessary, studies of hydrocarbon–water systems. Following Collander (33), who proposed that:

$$\log P_2 = a \log P_1 + b \qquad (12)$$

numerous demonstrations of the general validity of Eq. (12) have been provided. The greater the difference in nature between the organic phases 1 and 2, the poorer is the correlation. For example, correlation is good when oleyl alcohol and octanol are the two organic phases (77):

$$\log P_{ol} = 0.999 \log P_{oct} - 0.575 \qquad (33)$$

with
$$n = 37$$
$$r = 0.985$$
$$s = 0.225$$

On the other hand, in comparing, say, diethyl ether with octanol, satisfactory correlations can be obtained only after separation of solutes into hydrogen-bond donors and hydrogen-bond acceptors.

H-Bond Donors:

$$\log P_{ether} = 1.130 \log P_{oct} - 0.170 \qquad (34)$$

with
$$n = 71$$
$$r = 0.988$$
$$s = 0.186$$

H-Bond Acceptors:

$$\log P_{ether} = 1.142 \log P_{oct} - 1.070 \qquad (35)$$

with
$$n = 32$$
$$r = 0.957$$
$$s = 0.326$$

Leo, Hansch, and Elkins (71) reported that for a series of phenols:

$$\log P_{\text{oct}} = 0.50 \log P_{\text{cyclohexane}} + 2.43 \qquad (36)$$

with

$$n = 9$$
$$r = 0.791$$
$$s = 0.391$$

This poor correlation was much improved by adding a term K_{HB} to account for hydrogen bonding:

$$\log P_{\text{oct}} = 1.00 \log P_{\text{cyclohexane}} + 1.20 \log K_{\text{HB}} + 2.35 \qquad (37)$$

with

$$n = 9$$
$$r = 0.979$$
$$s = 0.140$$

Seiler (78) obtained similar good correlations by the use of another hydrogen bonding term, I_H.

Franke, Kühne, and Dove (72) recently carried out a principal components analysis of partition coefficients in six organic solvent–water systems. They found two principal components of partitioning behavior, the first being bulk (79) together with a polar contribution and the second being hydrogen bonding. They suggest that the hydrogen bonding can be accounted for by incorporating Seiler's I_H parameter (78), Rekker's key number correction (80) or indicator variables as suggested by Fujita et al. (81).

It will be seen from the above discussion that a great deal of consideration has been given to the use of different organic phases in partitioning studies. Little attention has been paid, however, to variations in the aqueous phase, to the extent that one can find the partition coefficients of ionizable compounds reported without even the pH being given.

Many partition coefficients are determined with a buffered aqueous phase, and it is not often realized that this can affect the values obtained. Davis et al. (82) showed that the octanol–water partition coefficient of phenol increased rectilinearly with ionic strength of the aqueous phase, this being presumably a salting-out effect. Wang and Lien (83) showed that the nature of the buffer affected the partition coefficient. Dearden and George (84) found that the error between measured true partition coefficients of a series of aspirin derivatives and those calculated from measurements of apparent partition coefficients at pH values of 4 and 6, increased with lipophilicity; they attributed this to ion-pair formation with the counterion of the buffer.

Solubility and Partitioning

Following Chiou, Schmedding, and Manes (85) we can write that for a solute distributed between two partially miscible phases at equilibrium:

$$x_o \gamma_o^* = x_w \gamma_w^* \qquad (38)$$

where x_o and x_w are the respective mole fractions and μ_o^* and μ_w^* the respective activity coefficients of the solute in the organic and aqueous phases. In dilute solution the mole fraction is equal to the molar concentration C multiplied by the molar volume V^* of each phase. Hence:

$$C_o \overline{V}_o^* \gamma_o^* = C_w \overline{V}_w^* \gamma_w^* \qquad (39)$$

Since partition coefficient P is defined (assuming the solute is present as a single species in both phases) as C_o/C_w, then:

$$P = \overline{V}_w^* \gamma_w^* / \overline{V}_o^* \gamma_o^* \qquad (40)$$

For a liquid solute of low solubility S_w in equilibrium with water, we can write:

$$x_s \gamma_s = x_w \gamma_w \qquad (41)$$

Assuming that water is only very slightly soluble in the liquid solute, both x_s and γ_s approximate to unity; writing

$$x_w = C_w \overline{V}_w = S_w \overline{V}_w \qquad (41)$$

it follows that:

$$S_w = 1/\gamma_w \overline{V}_w \qquad (42)$$

Note that V_w^* in Eq. (40) and V_w in Eq. (42) are equal if the organic phase is only negligibly soluble in water, as is the case with octanol, for example, at 4.5×10^{-3} M (33).

Combining Eqs. (40) and (42), we find that:

$$P = (1/S\overline{V}_o^* \gamma_o^*)(\gamma_w^*/\gamma_w) \qquad (43)$$

which transforms to:

$$\log P = -\log S_w - \log \overline{V}_o^* - \log \gamma_o^* + \log (\gamma_w^*/\gamma_w) \qquad (44)$$

If the solute forms an ideal solution in the organic phase, then $\gamma_o^* = 1$ and $\log \gamma_o^* = 0$; if the solubilities in water and in octanol-saturated water are the same, $\gamma_w^* = \gamma_w$ and $\log(\gamma_w^*/\gamma_w) = 0$. Hence a plot of $\log P$ versus $\log S_w$ should give a straight line with a slope of -1 and an intercept of $-\log V_o^*$.

Hansch, Quinlan, and Lawrence (86) found, for a wide range of liquid solutes, that:

$$\log S_w = -1.339 \log P + 0.978 \qquad (45)$$

with

$$n = 156$$
$$r = 0.935$$
$$s = 0.472$$

Similarly, Yalkowsky and Valvani (*87*) found:

$$\log x_w = -1.08 \log P - 1.04 \tag{46}$$

with

$$n = 417$$
$$r = 0.946$$
$$s = 0.356$$

where

$$\log x_w = \log S + \log \overline{V}_w$$

Again Tewari et al. (*88*), noting that $P = \gamma_w/\gamma_o$ (which assumes negligible mutual solubility of the two phases), and assuming that the variation of γ_o is very small compared with that of γ_w, found for a large number of liquid solutes:

$$\log P = 0.944 \gamma_w - 0.311 \tag{47}$$

with

$$n = 62$$
$$r = 0.990$$

For solid solutes, the situation is complicated by the fact that the crystal lattice must be disrupted in order for dissolution to occur. This can be allowed for in Eq. (42) by incorporating the ratio of fugacities of the solid and of its supercooled liquid:

$$S_w = (1/\gamma_w \overline{V}_w)(f_s/f_l) \tag{48}$$

where (*89*)

$$\log(f_s/f_l) = -(\Delta H_f/2.303R)[(T_m - T)/TT_m] \tag{49}$$

This is an entropic term ($\Delta S_f = \Delta_f/I_m$, where T_m is melting point), and Yalkowsky and Valvani (*87*) have discussed in detail the estimation of the entropy of fusion.

Neglecting, for reasons given above, the last two terms of Eq. (44) and incorporating the fugacity correction, we have:

$$\log S_w = -\log P - \log V_o^* - \left[\frac{\Delta H_f(T_m - T)}{2.303RTT_m}\right] \tag{50}$$

Estimating the entropy of fusion for rigid molecules, Yalkowsky and Valvani (*87*) formulated the expression:

$$\log S_w = -\log P - 0.01 \text{ MP} + 1.05 \tag{51}$$

where MP is the melting point on the centigrade scale and S_w is the molar solubility at 25°C. For a large number of rigid molecules, they found close agreement with Eq. (51):

$$\log S_w = -1.05 \log P - 0.012 \text{ MP} + 0.87 \tag{52}$$

with

$$n = 155$$
$$r = 0.989$$
$$s = 0.308$$

Yalkowsky and Valvani commend this equation as a means of estimating aqueous solubilities, which are notoriously difficult to determine for sparingly soluble compounds and even more difficult to predict from structural considerations.

On the less investigated question of solubility in the organic phase, Yalkowsky, Valvani and Roseman (*90*), on the assumption that octanol is an ideal solvent for the rigid, solid compounds they investigated, derived the equation:

$$\log x_o = -0.01 \text{ MP} + 0.25 \tag{53}$$

where MP is the melting point (centigrade) and solubility is measured at 30°C. Experimentally, they observed:

$$\log x_o = -0.012 \text{ MP} + 0.26 \tag{54}$$

with

$$n = 36$$
$$r = 0.92$$
$$s = 0.32$$

They also noted that:

$$\log P = 1.027 \log (S_o/S_w) \tag{55}$$

with

$$n = 36$$
$$r = 0.992$$
$$s = 0.326$$

That is, it is in order to take partition coefficient as the ratio of solubilities in octanol and water. It should be noted that this is not permissible if hydrocarbon organic phases are used, because of the likelihood of self-association. For example, Dearden and Langton (unpublished information) found that for alkylphenols in the cyclohexane-water system, S_o/S_w was 5 to 10 times the partition coefficient.

Intuitively, one would expect solubility in octanol to increase with partition coefficient. However, any such relationship is simply a measure of the deviation from ideality of the solution in the organic phase and ignores the entropy of fusion. Dobbs and Williams (*91*) report, for a number of pesticides and related compounds:

$$\log P_{oct} = -1.2 \log S + 6.8 \tag{56}$$

with

$$n = 12$$
$$r = 0.56$$

where S is the average solubility (in grams per liter) in a number of natural oils. The negative slope is probably inconsequential, bearing in mind that many of the solubilities were extremely high and that most of the solutes were solids.

In general then, solubility studies show that interactions in the aqueous phase, rather than the organic phase, control partitioning behavior.

Relationship of Partition Coefficient to Other Properties

Properties Affecting transport Within an Organism

The relationship of partition coefficient and aqueous solubility prompts a consideration of dissolution rate. The two are related by the Noyes-Whitney equation:

$$dc/dt = K(C_s - C) \qquad (57)$$

where C_s is the solubility and C is the concentration in solution at time t.

It might be considered, however, that dissolution rate is a more relevant parameter than is solubility, in transport of a xenobiotic in an organism. Save under equilibrium and steady-state conditions, biological response is time-dependent, and the rate at which a compound dissolves might be a predominant factor in transport, especially of very lipophilic compounds. Dearden and Patel (92) showed that, for a series of paracetamol (acetaminophen) derivatives, intrinsic aqueous dissolution rate constant (D) correlated better with partition coefficient than did solubility:

$$\log D = -0.990 \log P - 4.655 \qquad (58)$$

with
$$n = 6$$
$$r = 0.996$$
$$s = 0.106$$

$$\log S = -0.809 \log P - 2.806 \qquad (59)$$

with
$$n = 6$$
$$r = 0.944$$
$$s = 0.280$$

By the same token, it could be argued that partitioning rate constants are more relevant in QSAR studies than are partition coefficients. Lippold and Schneider (39) first showed that the water-organic phase transfer rate constant increases with partition coefficient, then levels off. The reverse is true for the organic phase–water transfer rate constant.

van de Waterbeemd (66) investigated partitioning rates in detail. He found that the plateau values of both forward and reverse rate constants were independent of the nature of the solute, but were dependent in the nature of the organic phase (Fig. 6). van de Waterbeemd et al. (49) envisaged stagnant diffusion layers on both sides of the water-organic phase interface; he considered (66) the plateau values shown in Figure 6 to be the diffusion rate constants in the stagnant layers, which would be expected to be more or less independent of molecular size, and therefore also of electronic properties such as would govern the extent of solvation.

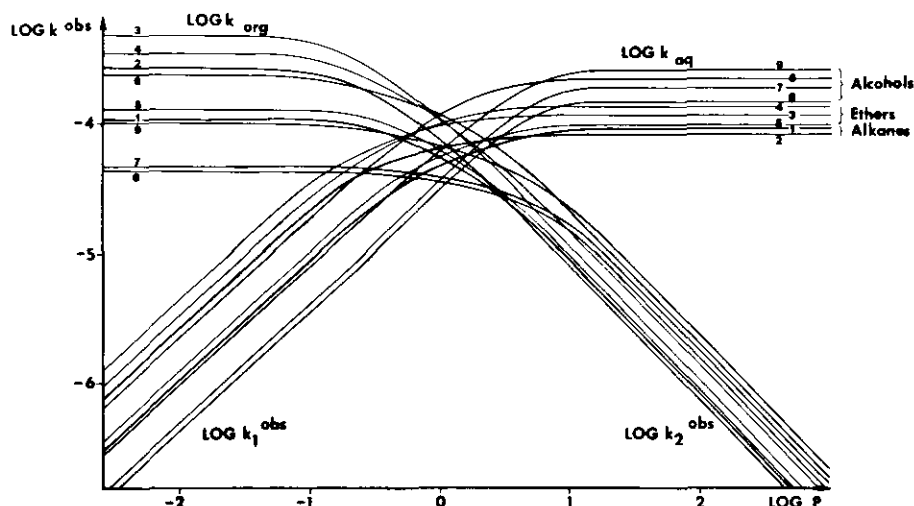However, if plateau levels related purely to stagnant

FIGURE 6.   Plots of log k^{obs} vs. log P in various organic solvent–water systems: (1) cyclohexane; (2) n-hexane; (3) diethyl ether; (4) diisopropyl ether; (5) di-n-butyl ether; (6) 1-hexanol; (7) cyclohexanol; (8) oleyl alcohol; (9) 1-octanol. From van de Waterbeemd (66) with permission.

layer diffusion, one would expect all k_{aq} values to be the same, irrespective of the nature of the organic phase (*93*). This is clearly not the case, as Figure 6 shows, although the range of plateau values is much smaller for k_{aq} than for k_{org}. Van de Waterbeemd (*66*) has noted in this connection that k_{aq} correlates with the difference in both the dielectric constant and the interfacial tension between the two phases, and de Haan and Jansen (*93*) have shown that:

$$\log k_{aq} = -1.008 \log \gamma_{aq} - 2.114 \qquad (60)$$

with

$$n = 9$$
$$r = 0.949$$
$$s = 0.061$$
$$F_{1,7} = 63.9$$

where γ_{aq} is the surface tension of water saturated with the appropriate solvent.

Kubinyi (*40*) has shown that relationships such as those shown in Figure 6 can, utilizing his bilinear equation [Eq. (27)], be described by:

$$k_1^{obs} = cP/(\beta P + 1) \qquad (61)$$

$$k_2^{obs} = C/(\beta P + 1) \qquad (62)$$

van de Waterbeemd (*66*) confirmed this experimentally; thus for a series of sulfonamides partitioning between water and octanol he found that:

$$\log k_1^{obs} = \log P - \log (\beta P + 1) - 3.996 \qquad (63)$$

with

$$n = 27$$
$$r = 0.993$$
$$s = 0.040$$

In this context also, van de Waterbeemd (*66*)showed that $\beta = k_{org}/k_{aq}$, so that β reflects the ratio of diffusion rate constants associated with the hydration-solvation process at the interface. This could well be expected to be related to viscosity and, as mentioned earlier, van de Waterbeemd (*66*) also found [Eq. (28)] that β was so related.

The importance of partitioning rate *in vivo* led Dearden and Bresnen (*94*) to examine whether partitioning rate constants gave better correlations than did partition coefficient with biological response measured at a fixed time after dosage. Using published analgesic activities of a series of paracetamol (acetaminophen) derivatives, they found that log k_2^{obs} correlated about as well as did log P, but that k_1^{obs} correlated very poorly. On the other hand, $\log (k_2^{obs}/k_1^{obs})$ (which should be equal to log P) correlated appreciably better than did log P obtained from measurements at equilibrium. Comments on these observations would be highly speculative at the moment, but the subject is worthy of further investigation.

The ability of a xenobiotic to bind to endogeneous protein will clearly affect its rate of progress through an organism. Generally, protein binding is to hydrophobic regions in proteins, so that one would expect a correlation between protein binding and lipophilicity. Many such relationships have been observed, the following example of neutral compounds binding to bovine serum albumin (*95*) being typical:

$$\log (1/C) = 0.751 \log P + 2.301 \qquad (64)$$

with

$$n = 42$$
$$r = 0.960$$
$$s = 0.159$$

where C is the concentration required to produce a 1:1 complex with protein.

The low regression coefficient of such correlations may be a pointer as to when protein binding plays a significant role in transport, because the regression coefficient of log P in a QSAR is expected to be unity when partitioning is the controlling factor (*38*).

Properties Relating to Bulk

Generally, as the size of an organic molecule increases, so does its lipophilicity, since the main molecular units are hydrocarbon in nature. One would, therefore, expect good correlations between partition coefficient and other parameters reflecting bulk, especially within an homologous series. Many such correlations have been observed, enabling such parameters to be used instead of lipophilicity in QSARs, and examples will be given of the most important of these.

Molecular weight (MW) is an obvious candidate property, being easy to obtain. Lien (*96*) has related the therapeutic doses of water-soluble vitamins in this way:

$$\log(1/C) = 3.830 \log MW - 2.630 \qquad (65)$$

with

$$n = 8$$
$$r = 0.992$$
$$s = 0.549$$
$$F_{1,6} = 34$$

Lien and Wang (*97*) have, however, pointed out that often the MW term has a significance beyond that of lipophilicity and this may be related to diffusion through liquids and to membrane clearance and perhaps renal clearance. For example, clearance (Cl) of drugs with MW < 1000 through artificial membranes is correlated thus:

$$\log Cl = -0.432 \log MW + 2.701 \qquad (66)$$

with

$n = 6$
$r = 0.997$
$s = 0.016$

Molar refractivity (MR) has the units of molar volume, but is considered (98) to possess a polarizability component, so that in fact it can be incorporated in a QSAR containing log P or π, so long as collinearity is low between the two sets of parameters. This is usually the case if polar compounds are included, but for apolar compounds MR correlates well with log P (99):

$$\log P = 0.70 \, (MR \times 10^{-1}) + 0.55 \qquad (67)$$

with

$n = 43$
$r = 0.951$
$s = 0.232$

Parachor (PA) similarly has units of molar volume, and Moriguchi (99) has shown a good correlation with lipophilicity for apolar compounds:

$$\log P = 1.04 \, (PA \times 10^{-2}) + 0.11 \qquad (68)$$

with

$n = 43$
$r = 0.955$
$s = 0.224$

Ahmad, Fyfe, and Mellors (100) have urged the use of parachor in QSAR studies because it has been shown to give good correlations and because it requires no experimental measurement. Briggs (32) gives a useful discussion of the calculation of parachor, its relationship to properties such as lipophilicity and water solubility and its application in environmental QSARs.

Naturally, molar volume itself would be expected to correlate with lipophilicity, and again Moriguchi (99) has confirmed this, although the correlation is poorer than those of Eqs. (67) and (68):

$$\log P = 0.27(MV \times 10^{-1}) - 0.04 \qquad (69)$$

with

$n = 43$
$r = 0.872$
$s = 0.367$

Moriguchi, Kanada, and Komatsu (101) showed that for apolar compounds, van der Waals volume (V_w) and van der Waals surface area (A_w) also correlated well with lipophilicity:

$$\log P = 2.51 \, V_w + 0.23 \qquad (70)$$

with

$n = 60$
$r = 0.980$
$s = 0.228$

$$\log P = 2.17 \, A_w - 0.04 \qquad (71)$$

with

$n = 60$
$r = 0.966$
$s = 0.295$

They then proceeded to work out correction terms for polar substituents. Leo, Hansch, and Jow (102) also found good rectilinear relationships between log P values and both molecular volumes and surface areas of apolar molecules.

Using cavity surface areas (CSA), Franke, Kühne, and Dove (72) found a good correlation with oleyl alcohol–water partition coefficients for a large number of compounds, including many polar compounds:

$$\log P_{ol} = 1.783 \, CSA - 4.291 \qquad (72)$$

with

$n = 50$
$r = 0.982$
$s = 0.154$

They point out that, unlike molar volume, molar refractivity and parachor, CSA group contributions reflect real solvation size properties, which is why the relationship holds for polar as well as apolar compounds.

Much interest has been created in recent years by the topological index called molecular connectivity. First devised by Randić (103), it was greatly extended by Kier and Hall (104). For nonpolar molecules, molecular connectivity is calculated as follows, taking n-pentane (A) and 2-methylbutane (B) as examples. The hydrogen-suppressed graphs of these compounds can be depicted by IA,B.

IA

IB
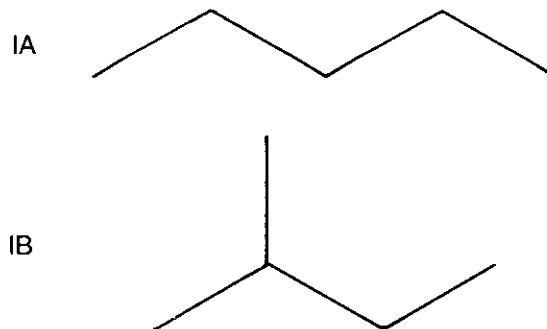
The numbers of nonhydrogen links formed by each atom are then added (II, B)

IIA

IIB
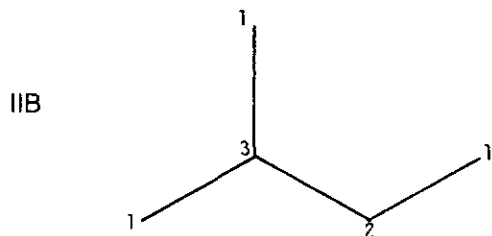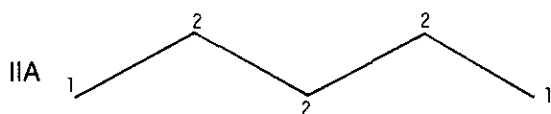
Adjacent values are then multiplied together to give IIIA,B.

IIIA

IIIB
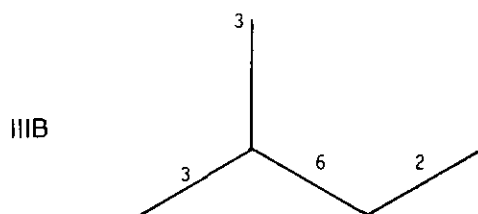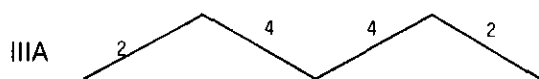
The reciprocal square roots of each number are then calculated and summed (IVA,B).

IVA

$\chi = 2.414$

IVB

$\chi = 2.269$

These values are termed first-order connectivities ($^1\chi$). Higher order connectivities can be calculated by calculating across two or more bonds. Heteroatoms are trea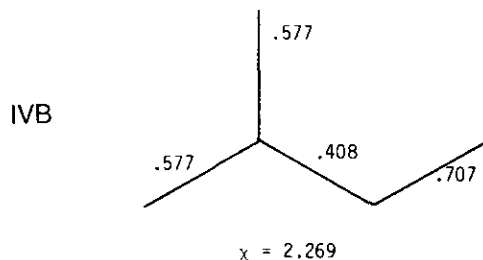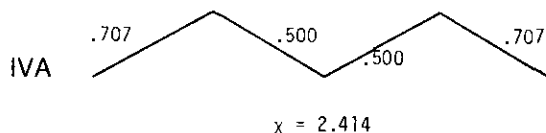ted by allocating them so-called valence values. The reader is referred to Kier and Hall (*104*) for a full explanation of this.

Molecular connectivity correlates well with lipophilicity, as Eq. (73) shows (*105*) for a range of polar com-

pounds including alcohols, ethers, esters, ketones, carboxylic acids and amines:

$$\log P = 0.950\,^1\chi - 1.48 \tag{73}$$

with

$$n = 138$$
$$r = 0.986$$
$$s = 0.152$$

Molecular connectivity is being increasingly applied to QSARs in environmental situations. For example, Sabljić and Protić (*106*) found for a series of chlorinated aromatic compounds:

$$\log BCF = -0.171(^2\overline{\chi}^V)^2 + 2.253(^2\overline{\chi}^V) - 2.392 \tag{74}$$

with

$$n = 17$$
$$r = 0.970$$
$$s = 0.297$$
$$F_{2,14} = 110.4$$

where BCF is the bioconcentration factor in fish and $^2\chi^V$ is the second-order valence connectivity.

More recently, Basak and co-workers have devised several topological indices which they term information content (IC), structure information content (SIC) and complementary information content (CIC). These are based on connections between atoms in a nonhydrogen-suppressed molecular graph; Basak and Magnuson (*107*) give details of the calculation of these indices. These authors report a good correlation between narcosis and CIC for an homologous series of aliphatic alcohols:

$$\log LC_{50} = -1.896\,CIC + 1.979 \tag{75}$$

with

$$n = 10$$
$$r = 0.989$$
$$s = 0.323$$
$$F_{1,8} = 355.3$$

It is not yet clear whether these indices can cope with the problem of heteroatom (polar group) substitution.

Cramer (*108*) recently introduced his *BC(DEF)* coordinates, where *B* and *C* are the axes of a plane in multidimensional space which best fits data from measured physical properties such as log *P*, MR, MV, MW and MP, each of which is represented by one axis in the space. It is remarkable that in the many sets of compounds examined by Cramer, such a *BC* plane has always been found. Cramer attributes the two coordinates *B* and *C*, which describe a compound's position in the plane, to bulk and cohesiveness. Deviations from the

plane, indicating specific interactions, are described by D, E and F coordinates. Cramer (109) has shown that the coordinates can well describe a wide range of biological activities and also (108) that they correlate well with the physical properties mentioned above. The correlation with octanol–water partition coefficient for a large number of compounds was:

$$\log P = 3.65B - 7.66C - 5.74D$$
$$- 0.31E + 5.09F + 1.60 \quad (76)$$

with

$$n = 114$$
$$r = 0.998$$
$$s = 0.08$$

It will no doubt be noted that numerous correlations of biological activity with physicochemical and structural properties include both a log P term and one of the parameters described above as being related to lipophilicity. This is, of course, quite acceptable, provided that there is no collinearity between the terms for the set of compounds or substituents examined. In such cases the second parameter represents some other property rather than, or as well as, lipophilicity.

Quantum Chemical Parameters

Lipophilicity has recently been correlated with quantum chemical parameters, and one could in a sense regard this as an attempt to factor lipophilicity into fundamental components [cf. the principal components analysis of Franke et al. (72), which factored lipophilicity into bulk and polarity and hydrogen bonding components]. Klopman and Iroff (110) obtained values close to experimental log P values by MINDO/3 and Hückeltype calculations of charge density. Zavoruev and Bolotin (111) found, for a series of substituted 1-phenyl-3,3-dimethyltriazenes:

$$\log P = -1.517 \, \Sigma |Q| + 1.428 \, S_t^N$$
$$- 13.332 \, Q_4 - 0.596 \quad (77)$$

with

$$n = 15$$
$$r = 0.899$$
$$s = 0.494$$
$$F_{3,11} = 15.5$$

where $\Sigma|Q|$ is the absolute total charge, S_t^N is the total nucleophilic superdelocalizability index, and Q_4 is the electrical charge at C^4.

Hopfinger and Battershell (112) have devised a method of predicting partition coefficients using a hydration shell model to compute the free energy of solvation as a function of conformation; this is not, however, a molecular orbital approach, as the only input required is molecular connection information.

It is to be hoped and expected that further research along similar lines will throw more light on the fundamental nature of lipophilicity.

Chromatographic Properties

All types of chromatography involve distribution between the mobile and stationary phases and so liquid–liquid chromatographic parameters, in particular, should be related to partition coefficient. Martin and Synge (113) showed that, for reversed-phase liquid–liquid chromatography (e.g., thin-layer):

$$P = K[(1/R_f) - 1] \quad (78)$$

where R_f is the ratio of distances moved by a compound and the solvent front in a given time. Bate-Smith and Westall (114) defined a parameter R_m as:

$$R_m = \log (1/R_f) - 1] \quad (79)$$

from which it follows that

$$R_m = \log P - \log K$$

In practice, the coefficient of log P varies, because the chromatographic partitioning system is varied to achieve a good range of R_f values. Many workers have shown excellent correlations between R_m and log P; Iwasa, Fujita, and Hansch (115) found for a series of substituted phenols:

$$\pi = -1.103 \, \Delta R_m + 0.647 \quad (80)$$

with

$$n = 12$$
$$r = 0.970$$
$$s = 0.051$$

ΔR_m is generally defined analogously to π; that is, $\Delta R_m = R_m$ (derivative) - R_m (parent). Clearly, in the case of Eq. (80), Iwasa et al. defined it oppositely, otherwise the sign of the regression coefficient of ΔR_m would be positive.

R_m has featured in many QSARs in lieu of log P. For example, Barbaro et al. (116) have recently reported the toxicities of xanthone derivatives:

$$\log (1/LD_{50}) =$$
$$-2.712 \, R_m^2 + 13.096R_m - 13.526 \quad (81)$$

with

$$n = 25$$
$$r = 0.848$$
$$s = 0.316$$
$$F_{2,22} = 28.1$$

Tomlinson (117) has reviewed the use of thin-layer R_m values in structure-activity studies.

The capacity factor k', equivalent to $[(1/R_f) - 1]$ in TLC, obtained from high-performance liquid chromatography may similarly be correlated with lipophilicity (118). Mirrlees et al. (119) used a kieselguhr column impregnated with water-saturated octanol. Unger, Cook, and Hollenberg (120), using an octanol-loaded C-18 Corasil column with methanol/water as the eluent, found for a range of different classes of compound that:

$$\log P = 1.025 \log k' + 0.797 \qquad (82)$$

with

$$n = 33$$
$$r = 0.987$$
$$s = 0.127$$
$$F_{1,31} = 1167$$

Lins et al. (121), in using HPLC to determine the lipophilicities of indolizine derivatives on a persilated column with 40%(v/v) acetonitrile/water as eluent [Eq. (83)],

$$\log P = 1.094 \log k' + 1.516 \qquad (83)$$

with

$$n = 6$$
$$r = 0.995$$
$$s = 0.045$$
$$F_{14} = 370$$

commented that the method was useful for obtaining log P values of relatively unstable compounds, since a chromatogram takes but a few minutes to obtain. Other advantages of chromatographic methods for obtaining log P are that compounds do not need to be pure and that replicates can be obtained quickly. There are, however, some disadvantages, such as the fact that the method is restricted to log P values in the range 0.5 to 2.5 (122) or 1.5 to 4 (123). Kaliszan (124) has recently reviewed the use of paper chromatography, TLC and HPLC in the determination of lipophilicity.

It might be thought that gas-liquid chromatography could not measure liquid–liquid partitioning behavior. However, Valko and Lopata (125) have shown that, if retention parameters (RP) are obtained using two columns differing in polarity, then log P can be related to the differences in π_{GLC} values. They found, for a series of substituted O-alkyl-O-aryl-phenylphosphonothioates, for example, that:

$$\log P = 2.180\pi_{GLC_1} - 1.385\pi_{GLC_2} + 0.039 \qquad (84)$$

with

$$n = 24$$
$$r = 0.965$$
$$s = 0.047$$
$$F_{2,21} = 140.7$$

where $\pi_{GLC} = \log(V_{N,X}/V_{N,H})$, V_N being the net retention volume, and subscripts 1 and 2 refer to polar and apolar stationary phases, respectively.

Valkó and Darvas (126) list the ten most suitable phase pairs for measuring partitioning behavior; the list is headed by Polyl 110/diethylene glycol succinate.

Chromatographic measures of lipophilicity are often found to correlate better with biological activities than do partition coefficients themselves, and it has been suggested that this may be because the dynamic nature of the chromatographic process is more akin to the penetration of a xenobiotic into an organism than is the statically measured partition coefficient (127).

Additive-Constitutive Nature of Partition Coefficient

In addition to demonstrating the quantitative description of biological activity in terms of physicochemical parameters, the Hansch school made another major contribution with their seminal paper (128) showing that log P was to a first approximation an additive property, but also had considerable constitutive character. By analogy with the Hammett equation (14), they defined a hydrophobic substituent constant, π, as:

$$\pi_X = \log (P_X/P_H) \qquad (85)$$

so that log P_X can be calculated as:

$$\log P_X = \log P_H + \pi_X \qquad (86)$$

Table 1. Some π-values derived from different series, in the octanol–water system.[a]

Substituent	Benzenes	Nitrobenzenes	Anilines	Phenols	Benzyl alcohols	Benzoic acids	Phenylacetic acids	Phenoxyacetic acids
4-CH$_3$	0.56	0.52	0.49	0.48	0.48	0.42	0.45	0.52
3-Cl	0.71	0.61	0.98	1.04	0.84	0.83	0.68	0.76
3-OH	−0.67	0.15	−0.73	−0.66	−0.61	−0.38	−0.52	−0.49
4-NO$_2$	−0.28	−0.39	0.49	0.50	0.16	0.02	−0.04	0.24

[a]Data from Fujita et al. (128).

Table 2. Methylene group contributions to partitioning (π-values) between various organic phases and water.[a]

Organic phase	Group contribution
Cyclohexane	0.64
Tetrachloromethane	0.62
Benzene	0.62
Diethyl ether	0.56
1-Octanol	0.50
Ethyl acetate	0.45
1-Butanol	0.44
3-Butanone	0.33

[a]Data from Davis et al. (129).

In so doing, they assumed that the series constant was unity, that is, that π_X had the same value irrespective of the series in which it was measured. That is approximately true for substituents which are incapable of hydrogen bonding, but not for others, as the data in Table 1 show. The hydrophobic constant also varies with the solvent pair used. Davis, Higuchi, and Rytting (129) report the values for methylene, some of which are shown in Table 2. It will be seen that, as expected, the more polar the organic phase the lower is the hydrophobic constant or group contribution to hydrophobicity, for methylene.

Fujita, Iwasa, and Hansch (128) showed that π-values in various series containing m- and p-substituents could be correlated through the use of the Hammett substituent constant σ, which is a measure of a substituent's electron-directing effect. For example:

$$\pi_{phenol} - \pi_{benzene} = 0.823\sigma + 0.061 \qquad (87)$$

with

$$n = 24$$
$$r = 0.954$$
$$s = 0.097$$

Franke (130) has found similar relationships using principal components analysis.

Similarly, Leo (131) has recently shown, for a large number of m- and p-disubstituted benzenes, that:

$$\log P_{obs} = 0.975 \log P_{add} + 0.849\rho_1\sigma_1 + 0.054 \qquad (88)$$

with

$$n = 196$$
$$r = 0.989$$
$$s = 0.118$$

where $\log P_{add}$ is the value calculated by adding π_X to $\log P_H$, and ρ_1 and σ_1 relate to the substituent in the parent molecule.

Fujita (132,133) has considered classes of aromatic compounds separately. For example, for nitrobenzenes he found:

$$\pi_{PhNO_2} = 0.913\pi_{benzene} - 0.139\sigma_X^0$$
$$+ 0.751\rho_X(m) + 0.751\rho_X(p) + 0.018 \qquad (89)$$

with

$$n = 28$$
$$r = 0.993$$
$$s = 0.063$$

Fujita quite rightly considers the effects of substitution to be bidirectional; that is, substituent X will modify the behavior of substituent Y and vice versa. He concludes, as did Leo (131), that the effects are almost entirely those of hydrogen bonding, with each substituent affecting the other's ability to interact with both water and octanol. Dunn, Johansson, and Wold (134) recently reached a similar conclusion following a principal components analysis of the log P values of 121 substituted benzenes.

Notwithstanding the above, π values in simple non-$ortho$-substituted aromatic compounds are approximately additive, and good estimates can be made of partition coefficients of derivatives, using published π values (135).

Hansch and Anderson (136) observed that the measured partition coefficients of compounds of the type $C_6H_5.CH_2.CH_2.CH_2.X$, where X is a polar group or atom, were lower than the values calculated by summation of π values. They attributed this to the side chain folding back so that substituent X interacted with the aromatic ring.

Nys and Rekker (137) suggested that the discrepancy observed by Hansch and Anderson between observed and calculated log P values was an artifact, arising from a neglect of the hydrophobic contribution of hydrogen; the Hansch system makes no distinction between, say, π_{CH2} and π_{CH3}. Indeed, Rekker (80) states that the Hansch system implies that:

$$\log P_{CH_4} = \pi_{CH_3} = \pi_{CH_2} \qquad (90)$$

Nys and Rekker (137,138) devised a new approach to additivity; they obtained fragmental hydrophobic constants (f values) by factoring large numbers of published log P values, so that:

$$\log P = \sum_1^n a_n f_n \qquad (91)$$

where a is a frequency factor indicating the incidence of a given fragment in the structure. For example (80), the log P of $(CH_3)_3CCH_2OCOCH_3$ is calculated as:

$$\log P = 4 f(CH_3) + f(CH_2) + f(C) + f(COO) \qquad (92)$$

Rekker (*80*) has pointed out that, while Eq. (86) is correct, the equation proposed by Tute (*44*):

$$\log P = \sum_{1}^{n} \pi_n \qquad (93)$$

is not, because of the incorrect assumption that $\pi_H = 0$. Thus one cannot write:

$$\log P(C_6H_5\text{---}CH_2\text{---}CH_3) =$$
$$\pi(C_6H_5) + \pi(CH_2) + \pi(CH_3) \quad (94)$$

or even

$$\log P(C_6H_5\text{---}CH_2\text{---}CH_3) =$$
$$\log P(C_6H_6) + \pi(CH_2) + \pi(CH_3) \quad (95)$$

Only the following Eq. (96) is correct:

$$\log P(C_6H_5\text{---}CH_2\text{---}CH_3) = \log P(C_6H_5\text{---}CH_3) + \pi(CH_3)$$
$$= \log P(C_6H_6) + 2\pi(CH_3)$$
$$(96)$$

It thus becomes evident, as Martin (*10*) has pointed out, that the π system is useful for calculating $\log P$ values of simple derivatives when the $\log P$ of the parent is known, but that the f system is far superior for major structural changes and for calculating $\log P$ values from scratch.

Rekker nevertheless found it necessary to introduce various correction factors to allow for such things as proximity effects, attachment of hydrogen to an electronegative center, and cross-conjugation. Diphenhydramine (V) serves as an example here.
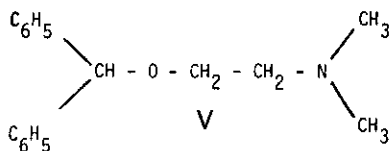
$$\log P = 2f(C_6H_5) + f(CH) + f(O) + 2f(CH_2)$$
$$+ f(N) + 2f(CH_3) + \text{p.e.2}$$
$$= 3.792 + 0.236 + (-1.536) + 1.054$$
$$+ (-2.133) + 1.404 + 0.46$$
$$= 3.28 \quad (\log P_{\text{obs}} = 3.27 \text{ and } 3.40)$$
$$(97)$$

The term p.e.2 is a proximity correction for a two-carbon separation of polar groups.

Rekker went on to point out that many of his cor-

rection factors were multiples (or approximately so) of 0.287; he termed this the magic constant C_M (an unfortunate name). Thus in the above example the proximity correction is approximately $2C_M$. Rekker later updated his f values by extending his analysis to a 1000 data set (*139*).

Following Nys and Rekker's publication of their f system (*137,138*), Leo et al. (*140*) also developed a fragmental constant system, but based on a synthetic approach rather than the analytical approach of Nys and Rekker. They carefully determined the partition coefficients of a number of small molecules, including hydrogen, from which they were able to obtain fragmental constants. Thus,

$$f_H = \tfrac{1}{2} \log P(H_2) = \tfrac{1}{2}(0.45) = 0.225 \qquad (98)$$

a value very close to that of 0.23 found by Nys and Rekker. Like Nys and Rekker, Leo et al. also found the necessity to introduce correction factors for such things as chain branching, fragments attached to aromatic rings, and the number of bonds between fragments. Full details of the method and examples of calculations are given by Hansch and Leo (*135*).

Janssen and Perrin (*141*) examined the theoretical basis of the π and f systems and concluded that they are based on the same assumption; they confirmed that for monovalent fragments:

$$f_X - \pi_X = f_H \qquad (99)$$

which Rekker (80) demonstrated experimentally. Mayer et al. (*142*) also compared the Rekker and Leo fragmental methods, and concluded that they are similar, differing perhaps only in starting point, and that at present they are not capable of predicting partition coefficients sufficiently accurately in all cases.

The systems devised by the Rekker and Hansch schools have provided the facility to calculate partition coefficients of small molecules reasonably accurately, provided that one is familiar with the methods of calculation and the applicability of the numerous correction terms; in the words of Mayer et al. (*142*), *a posteriori* manipulation of factors is necessary to approximate the observed $\log P$ value. Furthermore, they point out that neither method throws much light on the mechanism of partitioning (e.g., the fundamental reasons for the need for correction factors). Testa and Seiler (*143*) have factored Rekker's fragmental constant into a bulk (or steric, as they prefer to call it) and a polar or lipophobic component, in much the same way as has been done for π, but again this does not, as Testa and Seiler admit, tell us anything of the physical meaning of these factors.

Mayer et al. (*142*) have commented that every molecule is unique so far as geometry and charge distri-

Table 3. Some π-values for o- and p-methyl substitution.

Series	$\pi_{2\text{-}CH_3}$	$\pi_{4\text{-}CH_3}$	Reference
Phenoxyacetic acid	0.68	0.52	(128)
Benzoic acid	0.44	0.54	a
Acetanilide	–0.26	0.47	a
Aniline	0.34,0.50	0.43,0.49	(135)
N,N-Dimethylaniline	0.53	0.30	(135)
Chlorobenzene	0.58	0.47	(135)

[a]Data of J. C. Dearden and G. M. Bresnen (unpublished information).

Table 4. Effect of methyl substitution in phenol on log P.[a]

Compound	Log P (cyclohexane–water)	Log P (octanol–water)
Phenol	–0.74	1.46
2-Methylphenol	0.15	1.99
3-Methylphenol	–0.16	1.96
2,6-Dimethylphenol	0.97	2.22
3,5-Dimethylphenol	0.26	2.37

[a]Data of J. C. Dearden and G. M. Bresnen (unpublished information).

bution are concerned. Thus, while it is often instructive to seek for patterns in partitioning behavior, it is also helpful to examine specific molecules and to seek to interpret the partitioning behavior, perhaps with the help of other (e.g., spectroscopic) information, in terms of physicochemical phenomena.

An interesting example of the specific being unwarrantably generalized comes from the partition coefficient of o-methylphenoxyacetic acid. Fujita, Iwasa, and Hansch (128) reported $\pi_{2\text{-}CH_3}$ for this compound as 0.68, Hansch (128) appreciably higher than the normal $\pi_{2\text{-}CH_3}$ value (see Table 1). As that was the only $\pi_{2\text{-}CH_3}$ value they quoted, it became accepted as the definitive value. The situation was made worse by the value's being incorrectly quoted by Leo, Hansch, and Elkins (71) as 0.84, and this has been re-quoted (10,144). In fact, because of various shortrange interactions such as steric effects, inductive effects and intramolecular hydrogen bonding, π-values for *ortho* substituents in general vary appreciably. Table 3 shows some $\pi_{2\text{-}CH_3}$ values in various aromatic series. Dearden and Wootton (145) ascribed the very high $\pi_{2\text{-}CH_3}$ value in the phenoxyacetic acid series to steric enhancement of resonance. (They also confirmed the original value of 0.68.)

2-Substitution of any sort in acetanilides yields low π-values relative to 4-substitution, and Dearden and O'Hara (146) have shown that the discrepancy can be accounted for in terms of steric and inductive effects:

$$\pi_o = 0.716\pi_p + 0.357E_s - 0.291F + 0.020 \quad (100)$$

with

$$n = 12$$
$$r = 0.977$$

where F is the Swain and Lupton field factor (144).

Dearden and O'Hara (147) examined a series of 4-acetamidophenols and showed that the effect of methyl substitution adjacent to the acetamido group could be attributed to steric twisting of the group out of the plane of the ring; this was confirmed by ultraviolet spectroscopy. Dialkyl substitution adjacent to the hydroxyl group produces a lower than expected lipophilicity, due to shielding of the -OH group; the small water molecule is better able to interact with the shielded group than is the larger octanol molecule. This behavior, incidentally, is in marked contrast to that in the cyclohexane–water system, as the data in Table 4 show. In that system,

shielding produces a marked increase in lipophilicity. It cannot be decided, on these data alone, whether this is due to reduced affinity for water or increased affinity for cyclohexane. However, from a consideration of other information, Dearden and O'Hara (147) concluded that the latter was the case.

Lewis, Mirrlees, and Taylor (123,148) have elegantly rationalized the partition coefficients of nitrogen-containing heterocyclic compounds from a consideration of resonance, inductive, steric and hydrogen-bonding effects (separating the last into proton-donating and proton-accepting factors) and producing sets of equations for correction of heterocyclic π-values from the corresponding aromatic value.

Mayer et al. (149,150) have also investigated the partitioning behavior of nitrogen heterocyclics and found unexpectedly low log P values in some cases; they attribute this to an intramolecular interaction involving the chelation of a water molecule. The above examples indicate that it is possible to use partition coefficient as a structural tool, to provide information on, for example, aspects of molecular conformation.

Parker, Lemke, and Moore (151) raised the important concept of partition coefficient being conformation-dependent. For a series of hydroxyureas (RNHCONR'OH) they found that the nature and position of substitution affected the difference between observed and calculated log P values. Thus for R = Et, log P_{obs} was considerably more hydrophilic than calculated, which they postulated was due to the stabilization of forms such as VI.

VI
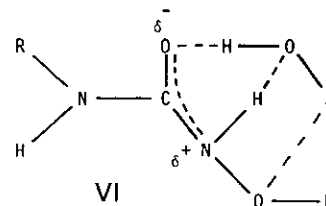
When R' = t-Bu, observed and calculated log P values were in close agreement, which the authors attributed to stabilization of an intramolecularly hydrogen-bonded form (VII).
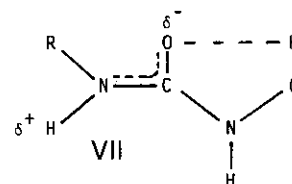

VII

Table 5. Thermodynamic parameters of transfer from water to octanol and cyclohexane.[a]

Compound	Octanol			Cyclohexane		
	$\Delta G°$, kJ/mole	$\Delta H°$, kJ/mole	$\Delta S°$, J/mole-°K	$\Delta G°$, kJ/mole	$\Delta H°$, kJ/mole	$\Delta S°$, J/mole-°K
p-Methylphenol	−16.4	08.4	+26.7	−3.6	+15.3	+63.4
p-Chlorophenol	−18.6	−10.5	+26.9	−2.8	+14.0	+56.4
p-Nitrophenol	−16.1	−19.2	−10.3	+6.4	+23.0	+55.5
p-Hydroxybenzaldehyde	−13.3	−9.6	+12.4	+8.5	+15.3	+22.8
p-Methylbenzoic acid	−18.7	−12.1	+22.0	−1.43	+6.7	+27.3

[a]Data of J. C. Dearden and G. M. Bresnen (158 and unpublished information). Values calculated on the mole fraction scale.

Davies, Sheard, and Taylor (152) point out that a minor conformer may sometimes be responsible for biological activity; if this is so, the overall partition coefficient (i.e., a weighted average over all conformers) will not predict activity well in a QSAR (unless the biologically active conformation is induced only by close approach to the receptor). These authors add that some measure of the active conformer fraction will be required in any comprehensive study of the relation between structure and activity. They do not speculate on how this is to be achieved, although NMR and IR probably offer the best opportunities at present for investigating conformation in solution. Yalkowsky and Valvani (153) have suggested that surface area calculations could provide a conceptual basis for understanding how conformation can affect partitioning.

Thermodynamic Studies of Partitioning

Log P is a free energy term and as such often hides more than it reveals (154). This is because free energy represents the difference between enthalpic and entropic contributions to a process:

$$\Delta G° = \Delta H° - T\Delta S° \qquad (101)$$

If enthalpy-entropy compensation occurs (155), then $\Delta G°$ can remain fairly constant despite variations in $\Delta H°$ and $\Delta S°$. An example of this comes from the work of Aveyard and Mitchell (156,157) who found greater positive enthalpies of transfer from water to hydrocarbon for alcohols than for carboxylic acids. This they attributed to dehydration of the hydroxyl group during transfer. Although this would occur also with the carboxylic acids, much of that would be recovered through dimerization in the hydrocarbon solvent. It should follow from this that the entropy of transfer should also be less for the acids, which was indeed found to be so.

At this point it is useful to consider briefly the processes involved in the transfer of a solute from aqueous to organic solution. In aqueous solution, any polar groups on the solute will form dipole-dipole interactions and hydrogen bonds with water. This will probably restrict rotational and perhaps translational freedom. If the sol-

Table 6. van't Hoff enthalpies of transfer of p-cresol from water to octanol and cyclohexane.

$\Delta H°$ kJ/mole	Organic phase	Reference
−8.7	Octanol	(159)
−8.4	Octanol	(158)
−7.3	Octanol	(161)
−8.8	Octanol	(162)
+15.3	Cyclohexane	a
+13.6	Cyclohexane	(161)
+18.6	Cyclohexane	(161)
+21.5	Cyclohexane	(163)
+25.5	Cyclohexane	(162)
+19.7	Cyclohexane	(164)
+17.2	Cyclohexane	(165)
+20.1	Cyclohexane	(164)[c]

[a]Data of J. C. Dearden and G. M. Bresnen (unpublished information).
[b]By two different van't Hoff methods.
[c]By calorimetry.

ute is wholly or partially nonpolar, water molecules will structure themselves around the solute, thus lowering the entropy of the system. On removal of the solute from the aqueous phase, any solute-solvent interactions must be broken and any water structuring is lost. The former has a positive $\Delta H°$, the latter a positive $\Delta S°$. However, the water cavity will close, so water-water bonds will form, with negative $\Delta H°$. On insertion of the solute into the organic phase, a cavity must form in the solvent ($\Delta H°$ positive). The solute will interact with the solvent ($\Delta H°$ negative, $\Delta S°$ negative). In the case of octanol and other solvents with dissolve appreciable concentrations of water, some of the solute-solvent interactions formed will again be with water. The data in Table 5 exemplify the above. Thus $\Delta S°$ is always greater for transfer to cyclohexane than to octanol; the difference is least for p-methylbenzoic acid, possibly because of dimerization in cyclohexane.

$\Delta H°$ is negative for transfer to octanol and positive for transfer to cyclohexane; that, there is net bond formation in the former and net bond breakage in the latter, reflecting cyclohexane's inability to interact strongly with solutes.

It is inappropriate here to consider the data in Table 5 in more detail, such as the negative entropy of transfer of p-nitrophenol to octanol (159). Furthermore, the data are undoubtedly subject to error. Beezer, Hunter, and Storey (160) have pointed out that, using the van't Hoff

method of determining $\Delta H°$, and error of $\pm$ 0.02 in log P could yield an error in $\Delta H°$ of $\pm$ 4.1 kJ/mole. To emphasize this point, Table 6 provides a compilation of enthalpies of transfer from water to octanol and cyclohexane; $\Delta G°$ and $\Delta S°$ values are not given because these are affected by the choice of concentration scale (molar, molal or mole fraction) used to report the partition coefficients. Jameson (166) has recently discussed the relative merits of the three scales.

Rogers and Wong (159) and James (161) have pointed out that thermodynamic analysis shows that the octanol–water system, on the whole, represents the biological membrane–water system better than does a hydrocarbon–water system.

Kinkel, Tomlinson, and Smit (167) have suggested that the van't Hoff method of determining thermodynamic parameters of partitioning in systems such as octanol–water will yield inaccurate results, because of the change in mutual solubility of the solvents with temperature. However, Beezer, Hunter, and Storey (160) have found excellent agreement between van't Hoff and calorimetric $\Delta H°$ values for alkoxyphenols partitioning between water and octanol; for example for m-methoxyphenol they report $\Delta H°$ (van't Hoff) = -7.9 kJ/mole and $\Delta H°$ (calorimetric) = -8.03 kJ/mole.

In a study of the thermodynamics of partitioning of resorcinol monoethers, Beezer, Hunter, and Storey (168) found that both $\Delta H°$ and $\Delta S°$ became increasingly positive as chain length increased. They attributed this to the alkyl chains disrupting octanol–octanol hydrogen bonding more than water–water hydrogen bonding. A more plausible explanation (161) is that there is increased water structuring around longer alkyl chains.

This example points up the inability even of a thermodynamic analysis of partitioning to explain fully the partitioning process, because each parameter reflects the difference between behavior in each phase, and says nothing about the absolute contribution of behavior in each phase. It has long been believed, for example, that aqueous phase behavior controls partitioning, via water structuring and hydrophobic bonding (169). However, Cramer (170) and Franke, Kühne, and Dove (72) have put forward evidence suggesting that solvation in the hydrophobic phase is more important than hydrophobic interactions in the aqueous phase. A thermodynamic study of liquid–liquid partitioning cannot clarify the situation. What is needed is a thermodynamic investigation of gas–water and gas–organic phase partition coefficients so that the contribution of each phase to the thermodynamics of transfer can be assessed.

Finally, an example is given of how a thermodynamic analysis of partitioning can help solve a problem. The octanol–water log P value of salicylic acid (2.24) is appreciably higher than is that of p-hydroxybenzoic acid (1.57), and this is attributed to the intramolecular hydrogen bond in the *ortho* isomer (71). However, log P for o-nitrophenol (1.79) is less than that for p-nitrophenol (1.91), and this has led Leo (131) and Fujita (132) to postulate that the intramolecular hydrogen bond in o-nitrophenol is broken in aqueous and octanol solution. A consideration of the thermodynamics of partitioning of the nitrophenols (Table 7) shows that this is not the case. $\Delta H°$ is much less negative and $\Delta S°$ much more positive for the *ortho* isomer, whereas one would have expected similarity of behavior with the other isomers, had the intramolecular hydrogen bond been broken. The lower $\Delta H°$ values shows that the ortho isomer is less able than are the other isomers to form hydrogen bonds with octanol, and the higher entropy change suggests either that there is more water-structuring of the other isomer, or less solute–octanol hydrogen bonding (giving rise to greater rotational and translational freedom), compared with the other isomers. All of these point towards the integrity of the intramolecular hydrogen bond in o-nitrophenol; in support of this it may be noted that the aqueous solubility of the *ortho* isomer is much lower than those of the other isomers (171).

General Conclusions

There is no more important parameter than lipophilicity in the quantitation of biological response, as a multiplicity of published QSARs attests. Other factors, such as electronic and steric effects both intra- and intermolecular, can affect the rate at which molecules arrive at a receptor site and the interaction with the receptor, but lipophilicity is generally dominant irrespective of the organism.

Partition coefficient is the most widely used measure of lipophilicity, and consequently the nature of the partitioning process has been extensively investigated. Various mathematical models of transport through alternate aqueous and lipid compartments in an organism have been devised and confirm, to a greater or lesser degree, experimentally observed QSARs. The most realistic model, based entirely on partitioning rates, is that of Penniston et al. (36), and we have shown that it can model not only QSARs but also duration of action and time to maximal response. The model thus confirms partitioning as the mechanism of transport of xenobiotics *in vivo*.

Partition coefficient is an additive/constitutive property and schemes devised by Rekker (80) and Hansch and Leo (135) permit the calculation of partition coefficients with reasonable accuracy in many cases, albeit with the aid of various correction factors.

Partition coefficient has been factored into bulk and hydrogen bonding components, and many other properties, such as molar volume, molecular surface area,

Table 7. Thermodynamics of transfer of nitrophenols from water to octanol.[a]

Isomer	$\Delta G°$, kJ/mole	$\Delta H°$, kJ/mole	$\Delta S°$, kJ/mole-°K
ortho	−15.4	−2.5	+43.3
meta	−16.2	−15.3	+3.0
para	−16.1	−19.2	−10.3

[a]Data of J. C. Dearden and G. M. Bresnen, (158 and unpublished information). Values calculated on the mole fraction scale.

parachor and molecular weight have been found to correlate with partition coefficient, for apolar molecules at least. Various topological indices have also been devised which correlate with partition coefficient. All of these parameters have been used successfully in place of, or in some cases in addition to, partition coefficient in QSARs.

Also used successfully to represent lipophilicity are parameters which themselves depend on partitioning, such as chromatographic parameters. Aqueous, but not organic phase, solubility can also be correlated with partition coefficient, and can thus be used as a lipophobicity parameter. Because partition coefficient is dependent on molecular configuration and conformation, it can be used as a structural tool, particularly when the enthalpy and entropy as well as the free energy of the partitioning process are studied.

REFERENCES

1. Crum Brown, A., and Fraser, T. R. On the connection between chemical constitution and physiological action I. On the physiological action of the salts of the ammonium bases, derived from strychnia, brucia, thebaia, codeia, morphia, and nicotia. Trans. Roy. Soc. Edinburgh 25: 151–203 (1868–1869).

2. Richardson, B. J. Physiological research on alcohols. Med. Times and Gazzette (ii): 703–706 (1869).

3. Richet, C. On the relationship between the toxicity and the physical properties of substances. Compt. Rend. Soc. Biol. (9)5: 775–776 (1893).

4. Overton, E. Osmotic properties of cells in the bearing on toxicology and pharmacology. Z. Physik. Chem. 22: 189–209 (1897).

5. Meyer, H. On the theory of alcohol narcosis I. Which property of anesthetics gives them their narcotic activity? Arch. Exper. Pathol. Pharmakol. 42: 109–118 (1899).

6. Berthelot, M., and Jungfleisch, E. On the laws that operate for the partition of a substance between two solvents. Ann. Chim. Phys. (4) 26: 396–407 (1872).

7. Leo, A. J. Relations between partitioning solvent systems. In: Biological Correlations—The Hansch Approach (R. F. Gould, Ed.), Adv. Chem. Ser. No. 114, American Chemical Society, Washington, DC, 1972, p. 51–60.

8. Nernst, W. Distribution of a substance between two solvents and between a solvent and steam. Z. Physik. Chem. 8: 110–139 (1891).

9. Ferguson, J. The use of chemical potentials as indices of toxicity. Proc. Roy. Soc. London B127: 387–403 (1939).

10. Martin, Y. C. Quantitative Drug Design. Marcel Dekker, New York, 1978.

11. Burger, A. Medicinal Chemistry, 2nd ed. Interscience, New York, 1960, p. 49.

12. Fieser, L. F., and Richardson, A. P. Naphthoquinone antimalarials II. Correlation of structure and activity against *P. lophurae* in ducks. J. Am. Chem. Soc. 70: 3156–3165 (1948).

13. Fieser, L. F., Ettlinger, M. G., and Fawaz, G. Naphthoquinone antimalarials.XV. Distribution between organic solvents and aqueous buffers. J. Am. Chem. Soc. 70: 3228–3232 (1948).

14. Hammett, L. P. Physical Organic Chemistry. McGraw-Hill, New York, 1940.

15. Purcell, W. P., Singer, J. A., Sundaram, K., and Parks, G. L. Quantitative structure-activity relationships and molecular orbitals in medicinal chemistry. In: Medicinal Chemistry, 3rd ed. (A. Burger, Ed.), Wiley-Interscience, New York, 1970, pp. 164–192.

16. Bruice, T. C., Kharasch, N., and Winzler, R. J. A correlation of thyroxine-like activity and chemical structure. Arch. Biochem. Biophys. 62: 305–317 (1956).

17. Zahradnik, R. Influence of the structure of aliphatic substituents on the magnitude of the biological effect of substances. Arch. Int. Pharmacodyn. Therap. 135: 311–329 (1962).

18. Free, S. M., and Wilson, J. W. A mathematical contribution to structure-activity studies. J. Med. Chem. 7: 395–399 (1964).

19. Hansch, C., Maloney, P. P., Fujita, T., and Muir, R. M. Correlation of biological activity of phenoxyacetic acids with Hammett substituent constants and partition coefficients. Nature 194: 178–180 (1962).

20. Hansch, C., and Fujita, T. ρ–σ–π analysis. A method for the correlation of biological activity and chemical structure. J. Am. Chem. Soc. 86: 1616–1626 (1964).

21. Hansch, C., and Dunn, W. J. Linear relationships between lipophilic character and biological activity of drugs. J. Pharm. Sci. 61: 1–19 (1972).

22. Hansch, C., and Clayton, J. M. Lipophilic character and biological activity of drugs II. The parabolic case. J. Pharm. Sci. 62: 1–21 (1973).

23. Purcell, W. P., and Testa, B. The development of bioactive compounds: a multidisciplinary approach. In: Biological Activity and Chemical Structure (J. A. Keverling Buisman, Ed.), Elsevier, Amsterdam, 1977, pp. 269–278.

24. Dearden, J. C., and George, E. Stability of aspirin derivatives to hydrolysis. Pharm. Acta Helv. 54: 347–348 (1979).

25. Fujita, T. The ortho effect in quantitative structure-activity correlations. Anal. Chim. Acta 133: 667–676 (1981).

26. Hansch, C., and Lien, E. J. An analysis of the structure-activity relationship in the adrenergic blocking activity of the β-haloalkylamines. Biochem. Pharmacol. 17: 709–720 (1968).

27. Topliss, J. G., and Costello, R. J. Chance correlations in structure-activity studies using multiple regression analysis. J. Med. Chem. 15: 1066–1069 (1972).

28. Li, R., Hansch, C., Matthews, D., Blaney, J. M., Langridge, R., Delcamp, T. J., Susten, S. S., and Freisheim, J. H. A comparison by QSAR, crystallography and computer graphics of the inhibition of various dihydrofolate reductases by 5(X-benzyl)-2,4-diaminopyrimidines. Quant. Struct.-Act.Relat. 1: 1–7 (1982).

29. Uchida, M., Funayama, S., and Sugimoto, T. Bioconcentration of fungicidal dialkyl dithiolanylidenemalonates in *Oryzias latipes* L. J. Pestic. Sci. 7: 181–186 (1982).

30. Egorova, N. A., Krasovskij, G. N., and Koch, R. Prediction of toxicity of chemical substances using structure-activity relationships. Chemosphere 11: 915–919 (1982).

31. Greenberg, M. J. Dependence of odor intensity on the hydrophobic properties of molecules. A quantitative structure–odor intensity relationship. J. Agr. Food Chem. 27: 347–352 (1979).

32. Briggs, G. G. Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors, and the parachor. J. Agr. Food Chem. 29: 1050–1059 (1981).

33. Collander, R. The partition of organic compounds between higher alcohols and water. Acta Chem. Scand. 5: 774–780 (1951).

34. Seeman, P., Roth, S., and Schneider, H. The membrane concentrations of alcohol anesthetics. Biochim. Biophys. Acta 225: 171–184 (1971).

35. Lien, E. J. Structure-absorption-distribution relationships: significance for drug design. In: Drug Design, Vol. 5 (E. J. Ariëns, Ed.), Academic Press, New York, 1975, pp. 81–132.

36. Penniston, J. T., Beckett, L., Bentley, D. L., and Hansch, C. Passive permeation of organic compounds through biological tissue: a non-steady state theory. Mol. Pharmacol. 5: 333–341 (1969).

37. Plá-Delfina, J. M., and Moreno, J. Intestinal absorption-partition relationships: a tentative functional non-linear model. J. Pharmacokin. Biopharm. 9: 191–215 (1981).

38. Seydel, J. K. Pharmacokinetics in drug design. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, pp. 163–181.

39. Lippold, B. C., and Schneider, G. F. Optimization of the availability of homologous quaternary ammonium compounds II. *In vitro* studies of the partition of N-(2-benzyloyloxyethyl)-N,N-dimethyl-N-alkylammonium bromides. Arzneim.-Forsch. 25: 843–852 (1975).

40. Kubinyi, H. Lipophilicity and drug activity. In: Progress in Drug Research, Vol. 23 (E. Jucker, Ed.), Birkhäuser, Basel, 1979, pp. 97–198.

41. Kubinyi, H. Lipophilicity and biological activity. Arzneim.-Forsch. 29: 1067–1080 (1979).

42. Dearden, J. C., and Townend, M. S. Duration of action of drugs as a function of lipophilicity. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, pp. 219–220.

43. Collander, R. The permeability of Nitella cells to non–electrolytes. Physiol. Plant. 7: 420–445 (1954).

44. Tute, M. S. Principles and practice of Hansch analysis. Guide to structure-activity correlation for the medicinal chemist. In: Advances in Drug Research, Vol. 6 (N. J. Harper and A. B. Simmonds, Eds.), Academic Press, London, 1971, pp. 1–77.

45. McFarland, J. W. On the parabolic relationship between drug potency and hydrophobicity. J. Med. Chem. 13: 1192–1196 (1970).

46. Higuchi, T., and Davis, S. S. Thermodynamic analysis of structure-activity relationships of drugs: prediction of optimal structure. J. Pharm. Sci. 59: 1376–1383 (1970).

47. Franke, R. Homologous species of hydrophobic compounds in the equilibrium between an aqueous and a hydrophobic phase. II. Biological activity and hydrophobic interactions with the receptor. Acta Biol. Med. Ger. 25: 789–803 (1970).

48. Yalkowsky, S. H., and Flynn, G. L. Transport of alkyl homologs across synthetic and biological membranes: a new model for chain length-activity relationships. J. Pharm. Sci. 62: 210–217 (1973).

49. van de Waterbeemd, H., van Boeckel, S., Jansen, A., and Gerritsma, K. Transport in QSAR II. Rate-equilibrium relationships and the interfacial transfer of drugs. Eur. J. Med. Chem. 15: 279–282 (1980).

50. Hansch, C. The use of substituent constants in drug modification. Farmaco, Ed. Sci. 23: 292–320 (1968).

51. Dearden, J. C. and Patel, K. D. Use of a physical multi-cell model to confirm theoretical predictions of biphasic structure-activity relationships. J. Pharm. Pharmacol. 30 (Suppl.): 51P (1978).

52. Hyde, R. M. Relationships between the biological and physicochemical properties of series of compounds. J. Med. Chem. 18: 231–233 (1975).

53. Martin, Y. C., and Hackbarth, J. J. Model-based linear free energy relationships of the biological activity of neutral and ionizable substances I. Equations for equilibrium-controlled potency. J. Med. Chem. 19: 1033–1039 (1976).

54. Moser, P., Jäkel, K., Krupp, P., Menasse, R., and Sallmann, A. Structure-activity relations of analogs of phenylbutazone. Eur. J. Med. Chem. 10: 613–617 (1975).

55. Dearden, J. C., and Townend, M. S. Digital computer simulation of the drug transport process. In: Quantitative Structure-Activity Analysis (R. Franke and P. Oehme, Eds.), Akademie-Verlag, Berlin, 1978, pp. 387–393.

56. Dearden, J. C., and Tomlinson, E. Buccal absorption as a parameter of analgesic activity of some p-substituted acetanilides. J. Pharm. Pharmacol. 23 (Suppl.): 73S–76S (1971).

57. Dearden, J. C., and O'Hara, J. H. Quantitative structure-analgesic activity studies of some alkyl derivatives of paracetamol (4-hydroxyacetanilide). J. Pharm. Pharmacol. 28 (Suppl.): 15P (1976).

58. Cooper, E. R., Berner, B., and Bruce, R. B. Kinetic analysis of relationship between partition coefficient and biological response. J. Pharm. Sci. 70: 57–59 (1981).

59. Dearden, J. C., and Townend, M. S. Computer modelling studies of time-variant biological response. Pestic. Sci. 10: 87–89 (1979).

60. Kutter, E., Herz, A., Teschemacher, H.-J., and Hess, R. Structure-activity correlations of morphine-like analgetics based on efficiencies following intravenous and intraventricular application. J. Med. Chem. 13: 801–805 (1970).

61. Dearden, J. C., and George, E. Quantitative structure-activity study of inhibition of blood platelet aggregation by aspirin derivatives. J. Pharm. Pharmacol. 29 (Suppl.): 74P (1977).

62. Herz, A., and Teschemacher, H.-J. Activities and sites of antinociceptive action of morphine-like analgesics and kinetics of distribution following intravenous, intracerebral and intraventricular application. In: Advances in Drug Research, Vol. 6 (N. J. Harper and A. B. Simmonds, Eds.), Academic Press, London, 1971, pp. 79–119.

63. Franke, R., and Kühne, R. Hydrophobic bonding in homologous series: an extended model. Eur. J. Med. Chem. 13: 399–402 (1978).

64. Dearden, J. C., O'Hara, J. H., and Townend, M. S. A double-peaked quantitative structure-activity relationship (QSAR) in a series of paracetamol derivatives. J. Pharm. Pharmacol. 32 (Suppl.): 102P (1980).

65. Kubinyi, H. Quantitative structure-activity relationships IV. Nonlinear dependence of biological activity on hydrophobic character: a new model. Arzneim.-Forsch. 26: 1991–1997 (1976).

66. van de Waterbeemd, H. The theoretical basis for relationships between drug transport and partition coefficients. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, pp. 183–192.

67. Berner, B., and Cooper, E. R. Application of diffusion theory to the relationship between partition coefficient and biological response. J. Pharm. Sci. 73: 102–106 (1984).

68. Wagner, J. G., and Sedman, A. J. Quantitation of rate of gastrointestinal and buccal absorption of acidic and basic drugs based on extraction theory. Pharmacokin. Biopharm. 1: 23–50 (1973).

69. Seydel, J. K., and Schaper, H.-J. Chemische Struktur und Biologische Aktivität von Wirkstoffen: Methoden de Quantitativen Struktur-Wirkungs-Analyse. Verlag Chemie, Weinheim, 1979.

70. Hansch, C., Muir, R. M., Fujita, T., Maloney, P. P., Geiger, F., and Streich, M. The correlation of biological activity of plant growth regulators and chloromycetin derivatives with Hammett constants and partition coefficients. J. Am. Chem. Soc. 85: 2817–2824 (1963).

71. Leo, A., Hansch, C., and Elkins, D. Partition coefficients and their uses. Chem. Rev. 71: 525–616 (1971).

72. Franke, R., Kühne, R., and Dove, S. Dependence of hydrophobicity on solvent and structure. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, pp. 15–32.

73. Lien, E. J., and Tong, G. L. Physicochemical properties and percutaneous absorption of drugs. J. Soc. Cosmet. Chem. 24: 371–384 (1973).

74. Brodin, A., Sandin, B., and Faijerson, B. Rates of transfer of organic protolytic solutes between an aqueous and an organic phase V. The thermodynamics of mass transfer. Acta Pharm. Suecica 13: 331–352 (1976).

75. Armstrong, N. A., Askam, V., Brain, K. R., Deol, G. K., and James, K. C. The stability of salsalate in octanol. J. Pharm. Pharmacol. 34 (Suppl.): 84P (1982).

76. Rytting, J. H., Davis, S. S., and Higuchi, T. Suggested thermodynamic standard state for comparing drug molecules in structure–activity studies. J. Pharm. Sci. 61: 816–818 (1972).

77. Leo, A., and Hansch, C. Linear free-energy relationships between partitioning solvent systems. J. Org. Chem. 36: 1539–1544 (1971).

78. Seiler, P. Interconversion of lipophilicities from hydrocarbon/water systems into the octanol/water system. Eur. J. Med. Chem. 9: 473–479 (1974).

79. Dunn, W. J., and Wold, S. Statistical analysis of the partition coefficient. Acta Chem. Scand. B32: 536–542 (1978).

80. Rekker, R. F. The Hydrophobic Fragmental Constant. Elsevier, Amsterdam, 1977.

81. Fujita, T., Nishioka, T. and Nakajima, M. Hydrogen-bonding parameter and its significance in quantitative structure-activity studies. J. Med. Chem. 20: 1071–1081 (1977).

82. Davis, S. S., Elson, G., Tomlinson, E., Harrison, G., and Dearden, J. C. The rapid determination of partition coefficient data using a continuous solvent extraction system (AKUFVE). Chem. Ind. (London) 1976: 677–683.

83. Wang, P.-H., and Lien, E. J. Effects of different buffer species on partition coefficients of drugs used in quantitative structure-activity relationships. J. Pharm. Sci. 69: 662–668 (1980).

84. Dearden, J. C., and George, E. Effect of lipophilicity of ionisable

drugs on deviations from expected pH-partition behaviour. J. Pharm. Pharmacol. 30 (Suppl.): 49P (1978).

85. Chiou, C. T., Schmedding, D. W., and Manes, M. Partitioning of organic compounds in octanol-water systems. Environ. Sci. Technol. 16: 4–10 (1982).

86. Hansch, C., Quinlan, J. E., and Lawrence, G. L. The linear free-energy relationship between partition coefficients and the aqueous solubility of organic liquids. J. Org. Chem. 33: 347–350 (1968).

87. Yalkowsky, S. H., and Valvani, S. C. Solubility and partitioning I: Solubility of non-electrolytes in water. J. Pharm. Sci. 69: 912–922 (1980).

88. Tewari, Y. B., Miller, M. M., Wasik, S. P., and Martire, D. E. Aqueous solubility and octanol/water partition coefficient of organic compounds at 25.0°C. J. Chem. Eng. Data 27: 451–454 (1982).

89. Hildebrand, J. H., Prausnitz, J. M., and Scott, R. L. Regular and Related Solutions. Van Nostrand-Reinhold, New York, 1970.

90. Yalkowsky, S. H., Valvani, S. C., and Roseman, T. J. solubility and partitioning VI: Octanol solubility and octanol-water partition coefficients. J. Pharm. Sci. 72: 866–870 (1983).

91. Dobbs, A. J., and Williams, N. Fat solubility–a property of environmental relevance? Chemosphere 12: 97–104 (1983).

92. Dearden, J. C., and Patel, N. C. Dissolution kinetics of some alkyl derivatives of acetaminophen. Drug Dev. Ind. Pharm. 4: 529–535 (1978).

93. de Haan, F. H. N. and Jansen, A. C. A. The influences of system variation on transport rate constants and transport rate parameters in organic solvent-water two-phase systems. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, pp. 215–216.

94. Dearden, J. C., and Bresnen, G. M. Partitioning rate constant as a parameter in quantitative structure-activity relationships (QSARs). J. Pharm. Pharmacol. 32 (Suppl.): 7P (1980).

95. Helmer, F., Kiehs, K., and Hansch, C. The linear free-energy relationship between partition coefficients and the binding and conformational perturbation of macromolecules by small organic compounds. Biochemistry 7: 2858–2863 (1968).

96. Lien, E. J. Molecular weights and therapeutic doses of drugs. J. Clin. Hosp. Pharm. 7: 101–106 (1982).

97. Lien, E. J., and Wang, P.-H. Lipophilicity, molecular weight, and drug action: re-examination of parabolic and bilinear models. J. Pharm. Sci. 69: 648–650 (1980).

98. Hansch, C. On the structure of medicinal chemistry. J. Med. Chem. 19: 1–6 (1976).

99. Moriguchi, I. Quantitative structure-activity studies I. Parameters relating to hydrophobicity. Chem. Pharm. Bull. Tokyo 23: 247–257 (1975).

100. Ahmad, P., Fyfe, C. A., and Mellors, A. Parachors in drug design. Biochem. Pharmacol. 24: 1103–1109 (1975).

101. Moriguchi, I., Kanada, Y., and Komatsu, K. van der Waals volume and the related parameters for hydrophobicity in structure-activity studies. Chem. Pharm. Bull. Tokyo 24: 1799–1806 (1976).

102. Leo, A., Hansch, C., and Jow, P. Y. C. Dependence of hydrophobicity of apolar molecules on their molecular volume. J. Med. Chem. 19: 611–615 (1976).

103. Randić, M. On characterization of molecular branching. J. Am. Chem. Soc. 97: 6609–6615 (1975).

104. Kier, L. B., and Hall, L. H. Molecular Connectivity in Chemistry and Drug Research. Academic Press, New York, 1976.

105. Murray, W. J., Hall, L. H., and Kier, L. B. Molecular connectivity III: relationship to partition coefficients. J. Pharm. Sci. 64: 1978–1981 (1975).

106. Sabljić, A., and Protić, M. Molecular connectivity: a novel method for prediction of bioconcentration factor of hazardous chemicals. Chem.-Biol. Interact. 42: 301–310 (1982).

107. Basak, S. C., and Magnuson, V. R. Molecular topology and narcosis. Arzneim.-Forsch. 33: 501–503 (1983).

108. Cramer, R. D. *BC(DEF)* parameters I. The intrinsic dimensionality of intermolecular interactions in the liquid state. J. Am. Chem. Soc. 102: 1837–1849 (1980).

109. Cramer, R. D. *BC(DEF)* correlation as a mechanistic probe in

biological systems. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, pp. 3–14.

110. Klopman, G., and Iroff, L. D. Calculation of partition coefficients by the charge density method. J. Comput. Chem. 2: 157–160 (1981).

111. Zavoruev, S. M., and Bolotin, V. A. Correlations between partition coefficients and quantum-chemical parameters of substituted 1-phenyl-3,3-dimethyltriazenes. Khim. Farm. Zh. 16: 1361–1364 (1982).

112. Hopfinger, A. J., and Battershell, R. D. Application of SCAP to drug design I. Prediction of octanol-water partition coefficients using solvent dependent conformational analyses. J. Med. Chem. 19: 569–575 (1976).

113. Martin, A. J. P., and Synge, R. L. M. A new form of chromatogram employing two liquid phases I. A theory of chromatography. II. Application to the microdetermination of the higher monoamino-acids in proteins. Biochem. J. 35: 1358–1368 (1941).

114. Bate-Smith, E. C., and Westall, R. G. Chromatographic behaviour and chemical structure I. Some naturally occurring phenolic substances. Biochim. Biphys. Acta 4: 427–440 (1950).

115. Iwasa, J., Fujita, T., and Hansch, C. Substituent constants for aliphatic functions obtained from partition coefficients. J. Med. Chem. 8: 150–153 (1965).

116. Barbaro, A. M., Guerra, M. C., Cantelli Forti, G., Aicardi, G., Biagi, G. L., Da Re, P., Valenti, P., and Borea, P. A. R_m values of xanthone derivatives in structure-activity studies. J. Chromatogr. 242: 1–7 (1982).

117. Tomlinson, E. Chromatographic hydrophobicity parameters in correlation analysis of structure-activity relationships. J. Chromatogr. 113: 1–45 (1975).

118. McCall, J. M. Liquid-liquid partition coefficients by high pressure liquid chromatography. J. Med. Chem. 18: 549–552 (1975).

119. Mirrlees, M. S., Moulton, S. J., Murphy, C. T., and Taylor, P. J. Direct measurement of octanol-water partition coefficients by high-pressure liquid chromatography. J. Med. Chem. 19: 615–619 (1976).

120. Unger, S. H., Cook, J. R., and Hollenberg, J. S. Simple procedure for determining octanol-aqueous partition, distribution and ionization coefficients by reversed phase high pressure liquid chromatography. J. Pharm. Sci. 67: 1364–1367 (1978).

121. Lins, C. L. K., Block, J. H., Doerge, R. F., and Barnes, G. J. Determination of octanol-water equivalent partition coefficients of indolizine and substituted 2-phenylindolizines by reversed-phase high-pressure liquid chromatography and fragmentation values. J. Pharm. Sci. 71: 614–617 (1982).

122. Anderson, N. H., James, M. J., and Davis, S. S. Uses of partition coefficients in the pharmaceutical industry. Chem. Ind. (London) 1981: 677–680.

123. Lewis, S. J., Mirrlees, M. S., and Taylor, P. J. Rationalisations among heterocyclic partition coefficients I. The π-value of phenyl. Quant. Struct.-Act. Relat. 2: 1–6 (1983).

124. Kaliszan, R. Chromatography in studies of quantitative structure-activity relationships. J. Chromatogr. 220: 21–83 (1981).

125. Valkó, K., and Lopata, A. Applicability of gas-liquid chromatography in determining liquid-liquid partition data. J. Chromatogr. 252: 77–90 (1982).

126. Valkó, K., and Darvas, F. Selection of GLC stationary-phase pairs for measuring log P. In: Quantitative Approaches to Drug Design (J. C. Dearden, Ed.), Elsevier, Amsterdam, 1983, p. 279.

127. Dearden, J. C., and Tomlinson, E. Correlation of chromatographically obtained substituent constants and analgesic activity. J. Pharm. Pharmacol. 24 (Suppl.): 115P–118P (1972).

128. Fujita, T., Iwasa, J., and Hansch, C. A new substituent constant, π, derived from partition coefficients. J. Am. Chem. Soc. 86: 5175–5180 (1964).

129. Davis, S. S., Higuchi, T., and Rytting, J. H. Determination of thermodynamics of the methylene group in solutions of drug molecules. J. Pharm. Pharmacol. 24 (Suppl.): 30P–46P (1972).

130. Franke, R. Theoretical Drug Design Methods. Elsevier, Amsterdam, 1984.

131. Leo, A. The octanol-water partition coefficient of aromatic sol-

utes: the effect of electronic interactions, alkyl chains, hydrogen bonds, and *ortho*-substitution. J. Chem. Soc. Perkin Trans. II (1983: 825–838 (1983).

132. Fujita, T. Substituent effects in the partition coefficient of disubstituted benzenes: bidirectional Hammett-type relationships. In: Progress in Physical Organic Chemistry, Vol. 14 (R. W. Taft, Ed.), Wiley, New York, 1983, pp. 75–113.

133. Fujita, T. Analysis and prediction of partition coefficients of meta- and para-disubstituted benzenes in terms of substituent effects. J. Pharm. Sci. 72: 285–289 (1983).

134. Dunn, W. J., Johansson, E., and Wold, S. Non-additivity of 1-octanol/water partition coefficients of disubstituted benzenes: an explanation and its consideration in log P estimation. Quant. Struct.-Act. Relat. 2: 156–163 (1983).

135. Hansch, C., and Leo, A. Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley, New York, 1979.

136. Hansch, C., and Anderson, S. M. The effect of intramolecular hydrophobic bonding on partition coefficients. J. Org. Chem. 32: 2583–2586 (1967).

137. Nys, G. G., and Rekker, R. F. Statistical analysis of a series of partition coefficients with special reference to the predictability of folding of drug molecules. Introduction of hydrophobic fragmental constants (*f* values). Chim. Ther. 8: 521–535 (1973).

138. Nys, G. G., and Rekker, R. F. Concept of hydrophobic fragmental constants (*f*-values) II. Extension of its applicability to the calculation of lipophilicities of aromatic and heteroaromatic structures. Eur. J. Med. Chem. 9: 361–375 (1974).

139. Rekker, R. F., and de Kort, H. M. The hydrophobic fragmental constant: an extension to a 1000 data point set. Eur. J. Med. Chem. 14: 479–488 (1979).

140. Leo, A., Jow, P. Y. C., Silipo, C., and Hansch, C. Calculation of hydrophobic constant (log P) from π and f constants. J. Med. Chem. 18: 865–868 (1975).

141. Janssen, L. H. M. and Perrin, J. H. Some theoretical observations on the estimation of partition coefficients from π and f constants Eur. J. Med. Chem. 11: 197–200 (1976).

142. Mayer, J. M., van de Waterbeemd, H., and Testa, B. A comparison between the hydrophobic fragmental methods of Rekker and Leo. Eur. J. Med. Chem. 17: 17–25 (1982).

143. Testa, B., and Seiler, P. Steric and lipophilic components of the hydrophobic fragmental constant. Arzneim.-Forsch. 31: 1053–1058 (1981).

144. Norrington, F. E., Hyde, R. M., Williams, S. G., and Wootton, R. Physicochemical-activity relations in practice I. A rational and self-consistent data bank. J. Med. Chem. 18: 604–607 (1975).

145. Dearden, J. C., and Wootton, J. C. Steric enhancement of resonance: an explanation of the anomalously high partition coefficients of some phenoxyacetic acids. J. Pharm. Pharmacol. 27 (Suppl.): 30P (1975).

146. Dearden, J. C., and O'Hara, J. H. Ortho-effects in structure-activity studies: correlation of π-values of o- and p-substituents in acetanilide. J. Pharm. Pharmacol. 27 (Suppl.): 29P (1975).

147. Dearden, J. C., and O'Hara, J. H. Partition coefficients of some alkyl derivatives of 4-acetamidophenol. Eur. J. Med. Chem. 13: 415–419 (1978).

148. Lewis, S. J., Mirrlees, M. S., and Taylor, P. J. Rationalisations among heterocyclic partition coefficients II. The azines. Quant. Struct.-Act. Relat. 2: 100–111 (1983).

149. Mayer, J. M., Testa, B., van de Waterbeemd, H., and Bornand-Crausaz, A. Non-additivity and intramolecular effects in the partition coefficient of ω-functionalized alkylpyridines. Eur. J. Med. Chem. 17: 453–459 (1982).

150. Mayer, J. M., Testa, B., van de Waterbeemd, H., and Bornand-Crausaz, A. Deviations in the log P of protonated arylalkylamines and in their apparent log P. Eur. J. Med. Chem. 17: 461–466 (1982).

151. Parker, G. R., Lemke, T. L., and Moore, E. C. Effect of solvent-dependent conformational system of hydroxyureas on predicted vs. observed log P. J. Med. Chem. 20: 1221–1225 (1977).

152. Davies, R. H., Sheard, B., and Taylor, P. J. Conformation, partition and drug design. J. Pharm. Sci. 68: 396–397 (1979).

153. Yalkowsky, S. H., and Valvani, S. C. Partition coefficients and surface areas of some alkylbenzenes. J. Med. Chem. 19: 727–728 (1976).

154. Franks, F., Ed. Water: A Comprehensive Treatise. Plenum Press, New York, 1975, pp. 1–94.

155. Tomlinson, E. Enthalpy-entropy compensation analysis of pharmaceutical, biochemical and biological systems. Int. J. Pharmaceutics 13: 115–144 (1983).

156. Aveyard, R., and Mitchell, R. W. Distribution of n-alkanols between water and n-alkanes. Trans. Faraday Soc. 65: 2645–2653 (1969).

157. Aveyard, R., and Mitchell, R. W. Distribution of n-alkanoic acids between water and n-alkanes. Trans. Faraday Soc. 66: 37–42 (1970).

158. Dearden, J. C., and Bresnen, G. M. Thermodynamics of partitioning—absence of constant hydrophobic effect of intramolecular hydrogen bonding. J. Pharm. Pharmacol. 34 (Suppl.): 82P (1982).

159. Rogers, J. A., and Wong, A. The temperature dependence and thermodynamics of partitioning of phenols in the n-octanol–water system. Int. J. Pharmaceutics 6: 339–348 (1980).

160. Beezer, A. E., Hunter, W. H. and Storey, D. E. Enthalpies of solution of a series of m-alkoxyphenols in water, n-octanol and water-n-octanol mutually saturated: derivation of the thermodynamic parameters for solute transfer between these solvents. J. Pharm. Pharmacol. 35: 350–357 (1983).

161. James, M. J. The thermodynamics of partitioning of phenolic compounds between aqueous solution and model membrane systems. Ph.D. Thesis, University of Nottingham, U.K., 1983.

162. Elson, G. N. The design and evaluation of an automated drug partitioning system for thermodynamic studies. M.Sc. Thesis, University of Aston, U.K., 1978.

163. Anderson, N. H., Davis, S. S., James, M., and Kojima, I. Thermodynamics of distribution of p-substituted phenols between aqueous solution and organic solvents and phospholipid vesicles. J. Pharm. Sci. 72: 443–448 (1983).

164. Huyskens, P. L. and Tack, J. J. Specific interactions of phenols with water. J. Phys. Chem. 79: 1654–1658 (1975).

165. Crugman, B. Thermodynamic quantities associated with the transfer of the methylene and oxygen functions from water to cyclohexane, and the temperature dependence of group contributions to partition coefficients. M.Sc. Thesis, University of Kansas, U.S.A., 1971.

166. Jameson, R. F. What concentration scale? What standard state? What species are present? In: Bioenergetics and Thermodynamics: Model Systems (A. Braibanti, Ed.), Reidel, Amsterdam, 1980, pp. 165–174.

167. Kinkel, J. F. M., Tomlinson, E., and Smit, P. Thermodynamics and extrathermodynamics of organic solute liquid-liquid distribution between water and 2,2,4-trimethylpentane. Int. J. Pharmaceutics 9: 121–136 (1981).

168. Beezer, A. E., Hunter, W. H. and Storey, D. E. Quantitative structure-activity relationships: the van't Hoff heats of transfer of resorcinol monoethers from water to n-octanol. J. Pharm. Pharmacol. 32: 815–819 (1980).

169. Ben-Naim, A. Hydrophobic Interactions. Plenum Press, New York, 1980.

170. Cramer, R. D. "Hydrophobic interaction" and solvation energies: discrepancies between theory and experimental data. J. Am. Chem. Soc. 99: 5408–5412 (1977).

171. Stephen, H., and Stephen, T., Eds. Solubilities of Inorganic and Organic Compounds. Pergamon Press, Oxford, 1963.